PHARMACEUTICAL COMPOSITIONS AND METHODS FOR THEIR USE

This application claims priority to United States Patent Application Nos. 60/449088, filed February 21, 2003, 60/472355, filed May 20, 2003, and 10/718337, filed November 19, 2003.

Field of the Invention

The present invention relates to pharmaceutical compositions and to methods for their use in decreasing cytochrome P450 (CYP450) enzyme activity. The present invention also relates to methods of increasing the bioavailability of a compound in a mammal. Additionally, the present invention relates to methods of decreasing the metabolism of certain compounds in a mammal that are metabolized by the cytochrome P450 enzyme. Furthermore, the present invention relates to pharmaceutical compositions comprising at least one compound metabolized by at least one cytochrome P450 enzyme and a cytochrome P450 enzyme-inhibiting amount of a compound of formula (I).

Background of the Invention

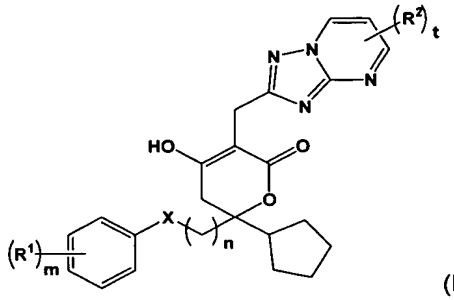
In mammals, the cytochrome P450 enzyme system comprises over 100 enzymes that modulate various physiological functions. In particular, the CYP450 enzymes are responsible for metabolizing xenobiotic substances so that they may be eliminated from systemic circulation. Most of the CYP450 enzymes responsible for metabolizing such substances in mammals are found in the liver.

It is known that some drugs, when administered to mammals, are metabolized by cytochrome P450 monooxygenase enzymes. The drug metabolites that result may, in some cases, be inactive in mammals and therefore may not produce a desired physiological effect. With some drugs, this metabolism by CYP450 enzymes to produce inactive metabolites may be so extensive that the pharmacokinetics of the drug are unfavorable, thereby requiring more frequent and higher doses of the drug than are desirable to achieve a desired physiological effect. Therefore, administration of such drugs in combination with an agent or agents that inhibit the CYP450 enzymes can improve the pharmacokinetics of such drugs by decreasing their metabolism by CYP450 enzymes. In turn, improved pharmacokinetics of a drug may have the advantages of decreasing both the dose and dosing frequency of the drug required to observe a desired physiological effect. Thus, the need exists for compounds that will inhibit CYP450 enzymes.

Summary of Invention

The present invention relates to methods of increasing the bioavailability in a mammal of a first compound which is metabolized by cytochrome P450, comprising

administering to said mammal said first compound and a cytochrome P450-inhibiting amount of a compound of formula (I),



(I)

wherein:

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from C_1-C_4 alkyl, and halogen;

X is $-CH_2-$ or $-O-$;

m is an integer from 0 to 5;

n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

It is to be understood that when t or m is an integer greater than 1, R^1 and R^2 may vary as a substituent or be the same. For example, where m is 2, the phenyl moiety to which R^1 is attached may be substituted with two different R^1 groups or two that are the same.

It is also to be understood that in the compounds of formula (I), when m is less than 5 and t is less than 3, the remaining positions on the phenyl and [1,2,4]triazolo[1,5a]pyrimidinyl rings, respectively, are substituted with hydrogen. For example, when m is 1, the remaining 4 positions on the phenyl ring contain hydrogen substituents. Similarly, when t is 1, for example, the remaining two positions on the [1,2,4]triazolo[1,5a]pyrimidinyl ring contain hydrogen substituents.

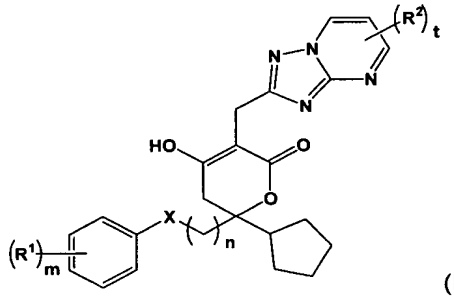
In another aspect of the present invention are provided methods of increasing the bioavailability in a mammal of a first compound which is metabolized by cytochrome P450, comprising administering to said mammal said first compound and a cytochrome P450-inhibiting amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the cytochrome P450 is the 2D6 isoform.

Also provided in the present invention are methods of increasing the bioavailability in a mammal of a first compound which is metabolized by cytochrome P450, wherein the first compound is selected from alprenolol, amiflamine, amitryptyline, aprindine, atomoxetine, bisoprolol, brofaromine, bufuralol, bunitrolol, bupronolol, captopril, chlorpheniramine,

chlorpromazine, cilostazol, cinnarizine, citalopram, clomipramine, clozapine, codeine, cyclobenzprine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, donezepil, doxepin, encainide, ethylmorphine, fenfluramine, flecainide, flunarizine, fluvoxamine, fluoxetine, fluphenazine, guanoxan, haloperidol, hydrocodone, imipramine, indoramin, labetalol, lidocaine, loratidine, maprotiline, (R)-methadone, meperidine, methamphetamine, methoxyamphetamine, 5-methoxyindoleethylamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, morphine, nefazodone, nelfinavir, norcodeine, nortryptyline, ondansetron, omeprazole, oxycodone, paclitaxel, paroxetine, perhexiline, perphenazine, phenformin, procodeine, promethazine, N-propylajmaline, propafenone, propanolol, retinoic acid, quinidine, risperidone, ritonavir, RU-486, sparteine, tamoxifen, testosterone, thioridazine, timolol, tolterodine, tomoxatene, tramadol, trazodone, trifluperidol, trimipramine, tropisetron, venlafaxine, vinblastine, and zuclopenthixol.

In still another aspect of the present invention are provided methods as above, wherein said first compound is chosen from antagonists of the N-methyl-D-aspartate receptor. In yet another aspect of the present invention are provided such methods wherein said antagonist of the N-methyl-D-aspartate receptor is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol, or a pharmaceutically acceptable salt or solvate thereof.

In another aspect of the present invention are provided methods of inhibiting cytochrome P450 activity in a mammal, comprising administering to said mammal a cytochrome P450 activity-inhibiting amount of a compound of formula (I),



(I)

wherein:

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from C_1-C_4 alkyl, and halogen;

X is $-CH_2-$ or $-O-$;

m is an integer from 0 to 5;

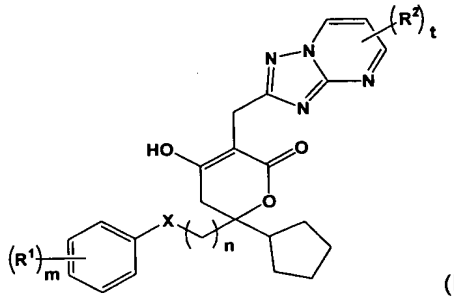
n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

Another aspect of the present invention provides methods of inhibiting cytochrome P450 enzyme activity in a mammal, comprising administering to said mammal a cytochrome P450 enzyme activity-inhibiting amount of a compound of formula (I), wherein the cytochrome P450 enzyme is the 2D6 isoform.

In yet another aspect of the present invention are provided methods of inhibiting cytochrome P450 enzyme activity, comprising contacting said cytochrome P450 enzyme with a cytochrome P450 enzyme-inhibiting amount of a compound of formula (I),



(I)

wherein:

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from C_1-C_4 alkyl, and halogen;

X is $-CH_2-$ or $-O-$;

m is an integer from 0 to 5;

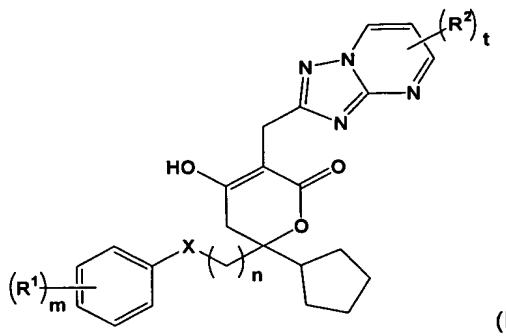
n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

In yet another aspect of the present invention are provided methods of inhibiting cytochrome P450 enzyme activity, comprising contacting said cytochrome P450 enzyme with a cytochrome P450 enzyme-inhibiting amount of a compound of formula (I), wherein the cytochrome P450 enzyme is the 2D6 isoform.

Still another aspect of the present invention provides methods of decreasing the metabolism in a mammal of a first compound which is metabolized by cytochrome P450, comprising administering to said mammal said first compound and a cytochrome P450-inhibiting amount of a compound of formula (I),



(I)

wherein:

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from C_1-C_4 alkyl, and halogen;

X is $-CH_2-$ or $-O-$;

m is an integer from 0 to 5;

n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

In still another aspect of the present invention are provided methods of decreasing the metabolism in a mammal of a first compound which is metabolized by cytochrome P450, comprising administering to said mammal said first compound and a cytochrome P450-inhibiting amount of a compound of formula (I), wherein the cytochrome P450 enzyme is the 2D6 isoform.

In another aspect of the present invention are provided any of above-described methods wherein in the compound of formula (I):

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from C_1-C_4 alkyl, and halogen;

X is $-CH_2-$;

m is an integer from 0 to 3;

n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

In yet another aspect of the present invention are provided any of the above-described methods wherein in the compound of formula (I):

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from C_1-C_4 alkyl, and halogen;

X is $-CH_2-$;

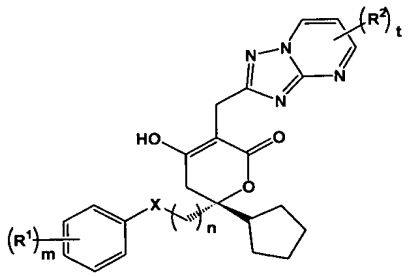
m is 1, 2 or 3;

n is 1;

t is 0, 1, or 2; and

pharmaceutically acceptable salts and solvates thereof.

In yet another aspect of the present invention are provided any of the above-described methods wherein the compound of formula (I) is selected from those of formula (Ia):



(Ia)

wherein:

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from C_1-C_4 alkyl, and halogen;

X is $-CH_2-$ or $-O-$;

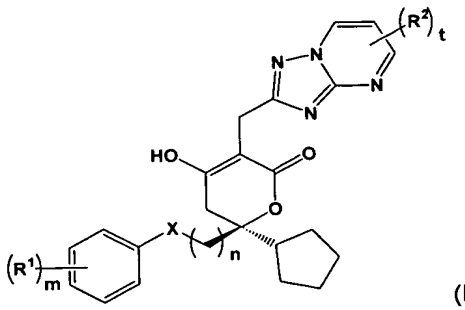
m is an integer from 0 to 5;

n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

Still another aspect of the present invention provides any of the above-described methods wherein the compound of formula (I) is selected from those of formula (Ib):



(Ib)

wherein:

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from C_1-C_4 alkyl, and halogen;

X is $-CH_2-$ or $-O-$;

m is an integer from 0 to 5;

n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

The present invention also provides any of the above-described methods wherein the compounds of formula (I) are selected from 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(3-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 6-[2-(3-chloro-5-ethyl-4-hydroxyphenyl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-

([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(4-methyl-1H-imidazol-5-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-({2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-({2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2,6-difluorophenyl)-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-5-(imidazo[1,2-a]pyridin-2-ylmethyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile; 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-{2-[3-fluoro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl}-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-5-[(6-ethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-

methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluoro-5-methoxyphenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; and pharmaceutically acceptable salts and solvates thereof.

In another aspect of the present invention are provided methods of decreasing the metabolism in a mammal of a first compound which is metabolized by cytochrome P450, wherein said first compound is chosen from antagonists of the N-methyl-D-aspartate receptor. Also provided in the present invention are such methods wherein said antagonist of the N-methyl-D-aspartate receptor is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol, or a pharmaceutically acceptable salt or solvate thereof.

Also provided in the present invention are any of the above-described methods wherein the compounds of formula (I) are selected from the (R)-enantiomers of 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(3-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 6-[2-(3-chloro-5-ethyl-4-hydroxyphenyl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{2-cyclopentyl-4-

hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(4-methyl-1H-imidazol-5-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-({2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-({2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2,6-difluorophenyl)-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-5-(imidazo[1,2-a]pyridin-2-ylmethyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile; 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-{2-[3-fluoro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl}-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-5-[(6-ethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-

methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluoro-5-methoxyphenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; and pharmaceutically acceptable salts and solvates thereof.

In yet another aspect of the present invention are provided any of the above-described methods wherein the compounds of formula (I) are selected from the (S)-enantiomers of 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(3-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 6-[2-(3-chloro-5-ethyl-4-hydroxyphenyl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-

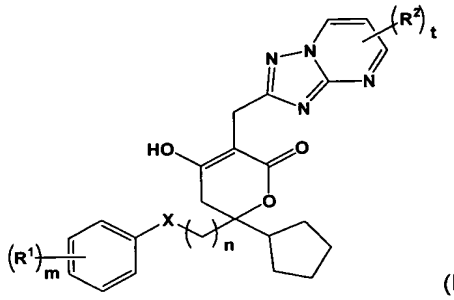
fluorophenyl)cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(4-methyl-1H-imidazol-5-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-({2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-({2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2,6-difluorophenyl)-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-5-(imidazo[1,2-a]pyridin-2-ylmethyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile; 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-{2-[3-fluoro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl}-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-5-[(6-ethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-

difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluoro-5-methoxyphenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; and pharmaceutically acceptable salts and solvates thereof.

In yet another aspect of the present invention are provided any of the methods described herein wherein the compound of formula (I) is substantially enantiomerically pure. Also provided herein are any of the methods described herein wherein the compound of formula (I) is enantiomerically pure.

It is understood that the present invention contemplates the use of any of the described embodiments of the compounds of formula (I) in any of the methods described herein.

In still another aspect of the present invention are provided compositions, comprising a first compound that is metabolized by at least one cytochrome P450 enzyme and a cytochrome P450 enzyme activity-inhibiting amount of a compound of formula (I),



(I)

wherein:

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from hydrogen, C_1-C_4 alkyl, and halogen;

X is $-CH_2$ or $-O-$;

m is an integer from 0 to 5;

n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

Also provided herein are compositions comprising a first compound that is metabolized by at least one cytochrome P450 enzyme and a cytochrome P450 enzyme activity-inhibiting amount of a compound of formula (I), wherein the at least one cytochrome P450 enzyme is the 2D6 isoform.

In another aspect of the present invention are provided such compositions, wherein the first compound that is metabolized by at least one cytochrome P450 enzyme is chosen from antagonists of the N-methyl-D-aspartate receptor. In a further aspect of the present invention are provided such methods wherein said antagonist of the N-methyl-D-aspartate receptor is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol, or a pharmaceutically acceptable salt or solvate thereof.

In yet another aspect of the present invention are provided compositions comprising a first compound that is metabolized by at least one cytochrome P450 enzyme and a cytochrome P450 enzyme activity-inhibiting amount of a compound of formula (I), wherein the first compound is selected from amitryptyline, bisoprolol, captopril, cilostazol, chlorpheniramine, chlorpromazine, citalopram, clomipramine, clozapine, codeine, cyclobenzprine, desipramine, dexfenfluramine, dextromethorphan, donezepil, doxepin, encainide, ethylmorphine, fenfluramine, flecainide, fluoxetine, fluphenazine, haloperidol, hydrocodone, imipramine, indoramin, labetalol, lidocaine, loratidine, maprotiline, (R)-methadone, meperidine, methamphetamine, metoprolol, mexiletine, morphine, nefazodone, nelfinavir, nortryptyline, ondansetron, omeprazole, oxycodone, paclitaxel, paroxetine, perphenazine, phenformin, propafenone, propanolol, retinoic acid, quinidine, risperidone, ritonavir, RU-486, tamoxifen, testosterone, timolol, tramadol, trazodone, trifluperidol, trimipramine, venlafaxine, and vinblastine.

In still another aspect of the present invention are provided any of the above-described compositions, wherein in the compound of formula (I):

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from hydrogen, C_1-C_4 alkyl, and halogen;

X is $-CH_2-$;

m is an integer from 0 to 3;

n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

Another aspect of the present invention provides any of the above-described compositions, wherein in the compound of formula (I):

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from hydrogen, C_1-C_4 alkyl, and halogen;

X is $-CH_2-$;

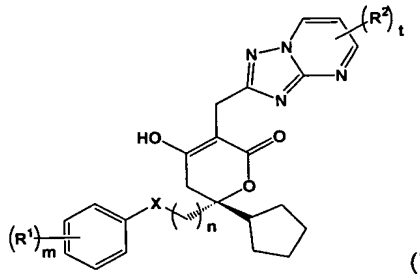
m is 1, 2 or 3;

n is 1;

t is 0, 1, or 2; and

pharmaceutically acceptable salts and solvates thereof.

Another aspect of the present invention provides any of the above-described compositions wherein the compound of formula (I) is selected from those of formula (Ia):



(Ia)

wherein:

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from hydrogen, C_1-C_4 alkyl, and halogen;

X is $-CH_2-$ or $-O-$;

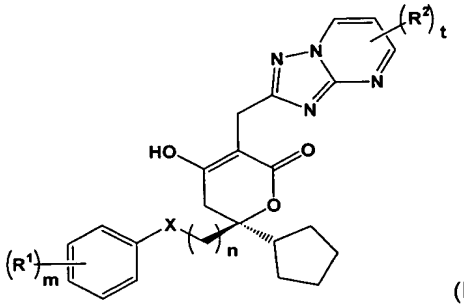
m is an integer from 0 to 5;

n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

In still another aspect of the present invention are provided any of the above-described compositions, wherein the compound of formula (I) is selected from those of formula (Ib):



(Ib)

wherein:

each R^1 is independently selected from fluorine, $-C(CH_3)_2CN$, -cyclopropyl-CN, and -cyclobutyl-CN;

each R^2 is independently selected from hydrogen, C_1-C_4 alkyl, and halogen;

X is $-CH_2-$ or $-O-$;

m is an integer from 0 to 5;

n is 1 or 2;

t is an integer from 0 to 3; and

pharmaceutically acceptable salts and solvates thereof.

Also provided herein are any of the above-described compositions, wherein the compound of formula (I) is selected from 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-[2-(3-ethyl-4-hydroxyphenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 6-[2-(3-chloro-5-ethyl-4-hydroxyphenyl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(4-methyl-1H-imidazol-5-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-

methylpropanenitrile; 2-[4-({2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-({2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2,6-difluorophenyl)-2-methylpropanenitrile; 2-(4-{2-[2-cyclopentyl-4-hydroxy-5-(imidazo[1,2-a]pyridin-2-ylmethyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile; 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-{2-[3-fluoro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl}-4-hydroxy-5,6-dihydro-2H-pyran-2-one; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile; 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-5-[(6-ethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]cyclopropanecarbonitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluoro-5-methoxyphenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-

2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile; and pharmaceutically acceptable salts and solvates thereof.. Also provided herein are any of the above-described compositions wherein the compound of formula (I) is chosen from the (R)- or the (S)-enantiomer. Additionally, the present invention provides compositions wherein the compound of formula (I) is substantially enantiomerically pure. Furthermore, the present invention provides compositions wherein the compound of formula (I) is enantiomerically pure.

It is to be understood that any of the compositions of the present invention can comprise any of the embodiments of the compounds of formula (I) described herein.

The term "cytochrome P450," as used herein, refers to a family of enzymes found in mammals that modulate various physiological functions. In mammals, these enzymes are found throughout various tissues. About 30 of the enzymes in the cytochrome P450 family are found primarily in the endoplasmic reticulum of hepatocytes in the liver and small intestine, with smaller quantities found in the kidneys, lungs, and brain (E.L. Michalets, *Review of Therapeutics, Update: Clinically significant cytochrome P450 drug interactions*, Pharmacotherapy, 1998, 18(1), pp. 84-122; T.F. Woolf, Handbook of Drug Metabolism, Marcel Dekker, Inc., New York, 1999. The term "isoform," as used herein, refers to a particular cytochrome P450 enzyme having a particular amino acid sequence. The terms, "cytochrome P450 2D6," "CYP 2D6," or "2D6," as used herein, refer to the cytochrome P450 enzyme with the amino acid sequence of the CYP 2D6 isoform, also known as debrisoquine hydroxylase, as described for the human population in Gonzalez, et al., *Nature* 331:442-446 (1988).

As used herein, the term "bioavailability" refers to the systemic availability of a given amount of a chemical compound administered to a mammal. Bioavailability can be assessed by measuring the area under the curve (AUC) or the maximum serum or plasma concentration (C_{max}) of the unchanged form of a compound following administration of the compound to a mammal. AUC is a determination of the Area Under the Curve plotting the serum or plasma concentration of a compound along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the AUC for a particular compound can be calculated using methods known to those of ordinary skill in the art and as described in G.S. Banker, Modern Pharmaceutics, Drugs and the Pharmaceutical Sciences, V. 72, Marcel Dekker, New York, Inc., 1996. The C_{max} value is defined as the maximum concentration of the compound achieved in the serum or plasma of a mammal following administration of the compound to the mammal. The C_{max} value of a particular compound can be measured using methods

known to those of ordinary skill in the art. The phrase "increasing bioavailability," as used herein means that the systemic availability of a first compound, measured as AUC or C_{max}, in a mammal is greater when co-administered with a compound of the present invention than when such co-administration does not take place.

The terms "administration", "administering", "dosage," and "dosing," as used herein refer to the delivery of a compound, or a pharmaceutically acceptable salt or solvate thereof, or of a pharmaceutical composition containing the compound, or a pharmaceutically acceptable salt or solvate thereof, to a mammal such that the compound is absorbed into the serum or plasma of the mammal.

The terms "co-administration" or "co-administering," as used herein, refer to the administration of a combination of a first compound and a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof. Such co-administration can be performed such that the first compound and the compound of the present invention are part of the same composition or part of the same unitary dosage form. Co-administration also includes administering a first compound and a compound of the present invention separately, but as part of the same therapeutic regimen. The two components, if administered separately, need not necessarily be administered at essentially the same time, although they can be if so desired. Thus co-administration includes, for example, administering a first compound and a compound of the present invention as separate dosages or dosage forms, but at the same time. Co-administration also includes separate administration at different times and in any order.

The term "first compound, " as used herein, refers to a compound for which it is desired to increase the bioavailability of or decrease the metabolism of using the methods of the present invention.

The terms "cytochrome P450-inhibiting amount" and "cytochrome P450 enzyme activity-inhibiting amount," as used herein, refer to an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, required to decrease the activity of cytochrome P450 enzymes or a particular cytochrome P450 enzyme isoform in the presence of such compound. Whether a particular compound of the present invention decreases cytochrome P450 enzyme activity, and the amount of such a compound required to do so, can be determined by methods known to those of ordinary skill in the art and the methods described herein.

The terms "inhibiting" or "inhibition," as used herein, refer to decreasing the activity of a cytochrome P450 enzyme or enzymes using compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof. Such inhibition may take place by the compound of formula (I) binding directly to the cytochrome P450 enzyme or enzymes. In addition, the activity of such cytochrome P450 enzymes may be decreased in the presence of a compound

of formula (I) when such direct binding between the enzyme and the compound of formula (I) does not take place. Furthermore, such inhibition may be competitive, non-competitive, or uncompetitive, as described in T.F. Woolf, Handbook of Drug Metabolism, Marcel Dekker, Inc., New York, 1999. Such inhibition may be determined using *in vitro* or *in vivo* systems, or a combination of both, using methods known to those of ordinary skill in the art.

The terms "metabolism" or "metabolizing," as used herein, refer to a process in which a compound is chemically modified by a biological system, such as *in vivo* in a mammal. Such modifications may also take place in certain *in vitro* systems known to those of ordinary skill in the art. Metabolism is generally described in T.F. Woolf, Handbook of Drug Metabolism, Marcel Dekker, Inc., New York, 1999.

The term "C_1-C_4 alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched, or cyclic moieties (including fused and bridged bicyclic and spirocyclic moieties), or a combination of the foregoing moieties, and containing from 1-4 carbon atoms. For an alkyl group to have cyclic moieties, the group must have at least three carbon atoms.

The terms "halogen" and "halo," as used herein represent fluorine, chlorine, bromine or iodine.

The term "cyano," as used herein, is meant to represent a group –CN.

The term "substituted" means that the specified group or moiety bears one or more substituents. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups, which may be present in the compounds of the present invention.

The term "solvate," as used herein, is intended to mean a compound of formula (I) in a form such that a molecule of solvent is associated with a molecule of formula (I). It is specifically contemplated that in the present invention one solvent molecule can be associated with one molecule of formula (I), such as a hydrate. Furthermore, it is specifically contemplated that in the present invention, more than one solvent molecule may be associated with one molecule of formula (I), such as a dihydrate. Additionally, it is specifically contemplated that in the present invention less than one solvent molecule may be associated with one molecule of formula (I), such as a hemihydrate. Furthermore, solvates of the present invention are contemplated as solvates of compounds of the present invention that retain the biological effectiveness of the non-hydrate form of the compounds.

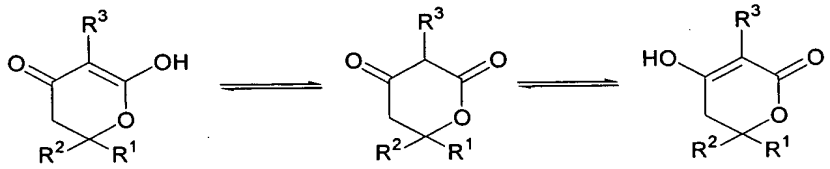
The term "substantially enantiomerically pure," as used herein, refers to a compound of formula (I) comprising at least about 90% of a single enantiomer (80% enantiomeric

excess). The term "enantiomerically pure," as used herein refers to a compound of formula (I) comprising at least about 95% of a single enantiomer (90% enantiomeric excess), or at least about 97.5% of a single enantiomer (95% enantiomeric excess.), or at least about 99% of a single enantiomer (98% enantiomeric excess).

The compound (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol can also be named as 1-[(1*S*,2*S*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]-4-phenylpiperidin-4-ol.

Detailed Description of the Invention

The compounds of the present invention may exist in several tautomeric forms. For example, a compound of the invention may exist in a form in which two ketones are present on a ring of the compound, as shown in (A) below. Alternatively, the compounds of the present invention may exist in at least two different enol forms, as shown in compounds (B) and (C) below. These three forms may be in equilibrium and the compounds of the invention may exist in more than one of these forms at the same time. For example, in a particular compound of the invention, a certain percentage of the molecules may be present in form (A) while the remainder are present in form (B) or form (C). Which form predominates in a particular compound of the invention depends on several factors that include, but are not limited to, whether the compound is in solid, liquid, or crystalline form, whether the compound is dissolved in a solvent and the identity of the solvent, the environmental temperature, and the relative humidity. It is specifically contemplated that when the compounds of the present invention are drawn in a particular form, form (A) for example, all the tautomeric forms, forms (B) and (C) for example, are included as well.



The compounds of the present invention may have asymmetric carbon atoms. The carbon-carbon bonds in the compounds of the present invention may be depicted herein using a solid line (———), a solid wedge (◀), or a dotted wedge (·····). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of the invention may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible

stereoisomers are meant to be included. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of the invention and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

Individual enantiomers of the compounds of the present invention can be designated as either the (R)- or (S)-enantiomer using conventional naming protocols known to those of ordinary skill in the art and as described in E.L. Eliel, et al., Stereochemistry of Organic Compounds, Wiley: New York, 1994. Furthermore, when a compound of the present invention contains more than one chiral carbon atom, the stereochemistry of the individual carbon atoms may be assigned as of either the (R)- or (S)-configuration according to methods known to those of ordinary skill in the art and as described in E.L. Eliel, et al., Stereochemistry of Organic Compounds, Wiley: New York, 1994.

Solutions of individual stereoisomeric compounds of the present invention may rotate plane-polarized light. The use of either a "(+)" or "(-)" symbol in the name of a compound of the invention indicates that a solution of a particular stereoisomer rotates plane-polarized light in the (+) or (-) direction, as measured using techniques known to those of ordinary skill in the art and as described in E.L. Eliel, et al., Stereochemistry of Organic Compounds, Wiley: New York, 1994.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Other methods of separating individual diastereomeric compounds are described in E.L. Eliel, et al., Stereochemistry of Organic Compounds, Wiley: New York, 1994. All such isomers, including enantiomeric mixtures, diastereomeric mixtures, and pure enantiomers are considered part of the present invention.

Alternatively, individual stereoisomeric compounds of the present invention may be prepared in enantiomerically enriched form by asymmetric synthesis, followed by purification as described above if necessary. Asymmetric synthesis may be performed using techniques known to those of ordinary skill in the art, such as the use of asymmetric starting materials that are commercially available or readily prepared using methods known to those of ordinary skill in the art, the use of asymmetric auxiliaries that may be removed at the completion of the synthesis, or the resolution of intermediate compounds using enzymatic methods. Other methods of preparing enantiomerically pure compounds are described in E.L. Eliel, et al., Stereochemistry of Organic Compounds, Wiley: New York, 1994. The choice of which

method is used will depend on factors that include, but are not limited to, the availability of starting materials, the relative efficiency of a method, and whether such methods are useful for the compounds of the invention containing particular functional groups. Such choices are within the knowledge of one of ordinary skill in the art.

When the compounds of the present invention contain asymmetric carbon atoms, the compounds, pharmaceutically acceptable salts or solvates may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates, and mixtures thereof are intended to be within the scope of the present invention.

As generally understood by those skilled in the art, an optically pure compound is one that is enantiomerically pure. As used herein, the term "optically pure" is intended to mean a compound comprising at least a sufficient activity.

If a derivative used in the method of the invention is a base, a desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid; hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid; and the like, or with an organic acid, such as acetic acid; maleic acid; succinic acid; mandelic acid; fumaric acid; malonic acid; pyruvic acid; oxalic acid; glycolic acid; salicylic acid; pyranosidyl acid, such as glucuronic acid or galacturonic acid; alpha-hydroxy acid, such as citric acid or tartaric acid; amino acid, such as aspartic acid or glutamic acid; aromatic acid, such as benzoic acid or cinnamic acid; sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid; and the like.

If a derivative used in the method of the invention is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative Examples of suitable salts include organic salts derived from amino acids such as glycine and arginine; ammonia; primary, secondary, and tertiary amines; and cyclic amines, such as piperidine, morpholine, and piperazine; as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include, but are not limited to, compounds of the invention in combination with water, isopropanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof.

A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified derivative, containing pharmacologically acceptable anions, and is not biologically or otherwise undesirable.

Examples of pharmaceutically acceptable salts include, but are not limited to, acetate, acrylate, benzenesulfonate, benzoate (such as chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, and methoxybenzoate), bicarbonate, bisulfate, bisulfite, bitartrate, borate, bromide, butyne-1,4-dioate, calcium edetate, camsylate, carbonate, chloride, caproate, caprylate, clavulanate, citrate, decanoate, dihydrochloride, dihydrogenphosphate, edetate, edislyate, estolate, esylate, ethylsuccinate, formate, fumarate, gluceptate, gluconate, glutamate, glycollate, glycollylarsanilate, heptanoate, hexyne-1,6-dioate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, γ-hydroxybutyrate, iodide, isobutyrate, isothionate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, mesylate, metaphosphate, methane-sulfonate, methylsulfate, monohydrogenphosphate, mucate, napsylate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phenylacetates, phenylbutyrate, phenylpropionate, phthalate, phospate/diphosphate, polygalacturonate, propanesulfonate, propionate, propiolate, pyrophosphate, pyrosulfate, salicylate, stearate, subacetate, suberate, succinate, sulfate, sulfonate, sulfite, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

It is understood by those of ordinary skill in the art that the compounds of the present invention, or their pharmaceutically acceptable salts or solvates, may exist in different polymorph or crystal forms, all of which are intended to be within the scope of the present invention and specified formulas. In addition, the compounds of the present invention, and their pharmaceutically acceptable salts and solvates, may exist as tautomers, all of which are intended to be within the broad scope of the present invention.

The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention can be prepared by treating the base compound with a substantially equivalent amount of the selected mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding an appropriate mineral or organic acid to the solution.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts

include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

Administration of the compounds, or their pharmaceutically acceptable salts or solvates, may be performed according to any suitable mode of administration available to one of ordinary skill in the art. Examples of such suitable modes of administration include oral, nasal, parenteral, topical, transdermal, rectal, or by inhalation or spray.

For example, such delivery may be performed by orally administering a first compound, or a pharmaceutically acceptable salt thereof, and a compound of the invention, or a pharmaceutically acceptable salt thereof, to a mammal, such as a human. Furthermore, the first compound and a compound of the present invention, and any additional compounds, may be administered in the form of a pharmaceutically acceptable formulation containing non-toxic, pharmaceutically acceptable carriers, adjuvants and vehicles. Alternatively, the first compound and a compound of formula (I), or pharmaceutically acceptable salts or solvates thereof, may be administered to a mammal by other routes of administration including, but not limited to, intravenous, topical, sublingual, parenteral, rectal, or by inhalation or spray. Such alternative administration may be performed with the first compound and a compound of the present invention alone or in dosage unit formulations containing non-toxic, pharmaceutically acceptable carriers, adjuvants and vehicles. In addition, the present invention specifically contemplates that the first compound and the compound of the present invention may be co-administered using different forms of administration for each. For example, the first compound may be administered topically while the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, may be administered orally. The preferred formulation and route of administration of the first compound and the compound of the present invention to a mammal will depend on the age and condition of the mammal, the condition being treated, the identity of the first compound, the identity of the compound of the present invention, and other factors known to those of ordinary skill in the art. The

formulation and route of administration can be determined by one of ordinary skill in the art without undue experimentation.

Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions are known or may be routinely determined by those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural, and/or rectal administration.

Pharmaceutical compositions of the invention may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use. Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles, or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid. Illustrative liquid carriers include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged-release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g., solution), or a nonaqueous or aqueous liquid suspension.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition, 1975.

It will be appreciated that the actual dosages of the compounds of the present invention, or pharmaceutically acceptable salts thereof, used in the pharmaceutical compositions of this invention will be selected according to the properties of the particular agent being used, the particular composition formulated, the mode of administration, the particular site, the host, and the condition being treated. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage-determination tests. For oral administration, e.g., a dose that may be employed is from about 0.001 to about 1000 mg/kg body weight, preferably from about 0.1 to about 100 mg/kg body weight, and even more preferably from about 1 to about 50 mg/kg body weight, with courses of treatment repeated at appropriate intervals.

The amount and timing of compounds administered will, of course, be based on the judgement of the prescribing physician. Thus, because of subject-to-subject variability, the dosages provided are a guideline and one of ordinary skill in the art may titrate doses of the

agent to achieve the activity that they consider appropriate for the individual subject. In considering the degree of activity desired, one of skill in the art must balance a variety of factors such as cognitive function, age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular).

The compositions of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable vehicle or diluent. Thus, the compounds of this invention can be administered individually or together with the first compound(s) in any conventional dosage form.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques known to those skilled in the art.

For purposes of transdermal (e.g., topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition, 1975.

The compounds of the present invention can be prepared by procedures known to those of ordinary skill in the art and as described in co-pending United States Patent Application No. 10/718,337, which is hereby incorporated by reference.

Procedures

Specific Examples of various compounds according to the invention may be advantageously prepared as set out in the Examples above.

The structures of the compounds of the following Examples were confirmed by one or more of the following: proton magnetic resonance spectroscopy, infrared spectroscopy, elemental microanalysis, mass spectrometry, thin layer chromatography, melting point, boiling point, and HPLC.

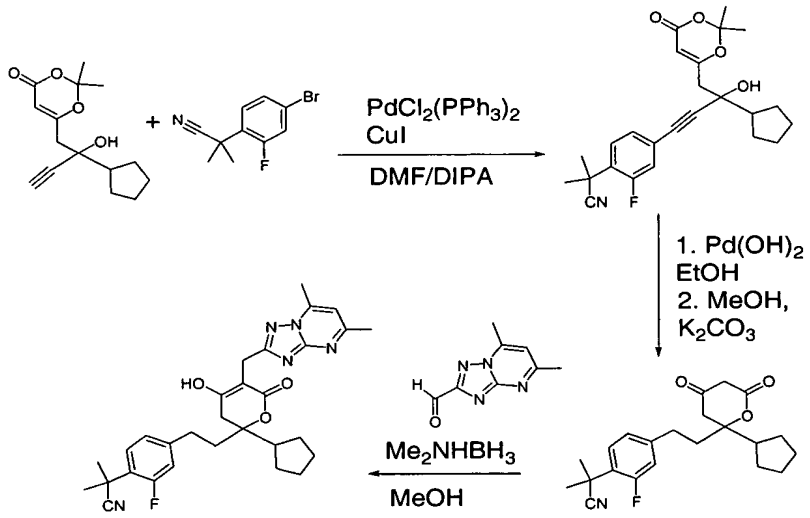
Proton magnetic resonance (^{1}H NMR) spectra were determined using a 300 megahertz Tech-Mag, Bruker Avance 300DPX, or Bruker Avance 500 DRX spectrometer operating at a field strength of 300 or 500 megahertz (MHz). Chemical shifts are reported in parts per million (ppm, ?) downfield from an internal tetramethylsilane standard. Alternatively, ^{1}H NMR spectra were referenced to residual protic solvent signals as follows: $CHCl_3$ = 7.26 ppm; DMSO = 2.49 ppm; C_6HD_5 = 7.15 ppm. Peak multiplicities are designated as follows: s = singlet; d = doublet; dd = doublet of doublets; t = triplet; q = quartet; br = broad resonance; and m = multiplet. Coupling constants are given in Hertz. Infrared absorption (IR) spectra were obtained using a Perkin-Elmer 1600 series FTIR spectrometer. Elemental microanalyses were performed by Atlantic Microlab Inc. (Norcross, GA) and gave results for the elements stated within ±0.4% of the theoretical values. Flash column chromatography was performed using Silica gel 60 (Merck Art 9385). Analytical thin layer chromatography (TLC) was performed using precoated sheets of Silica 60 F_{254} (Merck Art 5719). HPLC chromatographs were run on a Hewlett Packard Model 1100 system fitted with a Zorbax SB-C18 4.6 mm x 150 mm column having 3.5 micron packing material. Unless otherwise stated, a ramp of 5% CH_3CN/H_2O to 95% CH_3CN/H_2O over 7.5 minutes then holding at 95% CH_3CN/H_2O for 2.5 minutes (both solvents contained 0.1% v/v TFA) at a flow of 1 mL/min was used. Retention times (Rt) are given in minutes. Semi-preparative HPLC samples were run on a Gilson LC3D system fitted with a 21.2 mm x 250 mm C8 column. Ramps were optimized for each compound with a CH_3CN/H_2O solvent system. Melting points were determined on a Mel-Temp apparatus and are uncorrected. All reactions were performed in septum-sealed flasks under a slight positive pressure of argon, unless otherwise noted. All commercial reagents were used as received from their respective suppliers with the following exceptions: tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl prior to use; dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use; anhydrous lithium chloride was prepared by heating at 110°C under vacuum overnight. Mass spectra,

both low and high resolution, were measured using either electrospray (EI) or fast atom bombardment (FAB) ionization techniques.

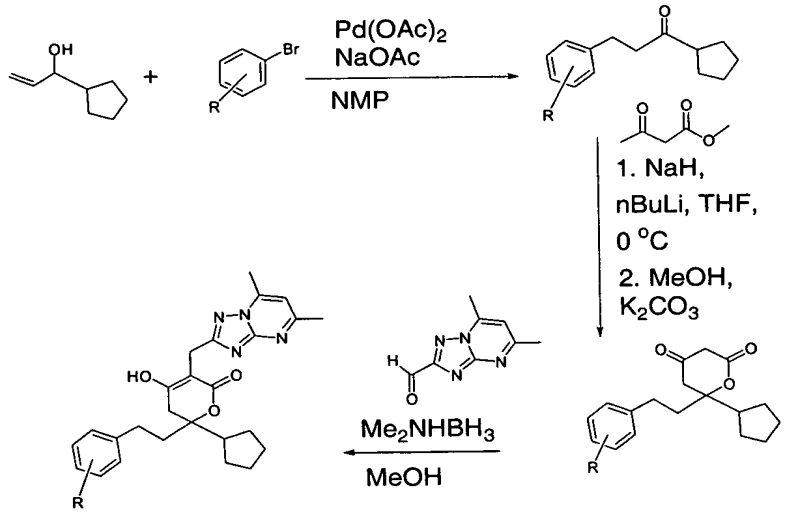
The following abbreviations are used herein: Et_2O (diethyl ether); DMF (*N,N*-dimethylformamide); DMSO (dimethylsulfoxide); MeOH (methanol); EtOH (ethanol); EtOAc (ethyl acetate); Ac (acetyl); Hex (hexane); Me (methyl); Et (ethyl); Ph (phenyl); DIEA (diisopropylethylamine); TFA (trifluoroacetic acid); DTT (dithiothreitol); and THF (tetrahydrofuran); and (precipitate); min. or min (minutes); h (hours).

Solid-phase syntheses were performed by immobilizing reagents with Rink amide linkers (Rink, *Tetrahedron Letters* (1987) 28:3787), which are standard acid-cleavable linkers that upon cleavage generate a free carboxamide group. Small-scale solid-phase syntheses, e.g., about 2 – 5 μmole, were performed using Chiron SynPhase® polystyrene O-series crowns (pins) derivatized with Fmoc-protected Rink amide linkers. For larger scale (e.g., greater than about 100 μmole) syntheses, the Rink amide linkages were formed to Argonaut Technologies Argogel® resin, a grafted polystyrene-poly(ethylene glycol) copolymer. Any suitable resin may be used as the solid phase, selected from resins that are physically resilient and that, other than with regard to the linking and cleavage reactions, are inert to the synthetic reaction conditions.

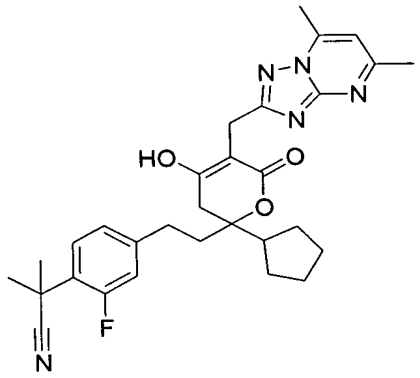
Scheme 1. Sonogashira route:



Scheme 2. Heck route:



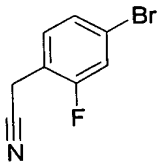
Example 1: 2-(4-{2-[2-Cyclopentyl-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]-ethyl}-2-fluoro-phenyl)-2-methyl-propionitrile



To a solution of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile (0.40 g, 1.1 mmol) from Step 4 below, in MeOH (7 mL) was added 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (0.19 g, 1.08 mmol), described in Step 7 below and borane-dimethylamine complex (76 mg, 1.3 mmol) and stirred at room temperature for 3 hours. The reaction was quenched with 10 mL saturated NH_4Cl and 5 mL water. To this was added 20 mL CH_2Cl_2 and the pH of the aqueous phase was adjusted to 3. The layers were separated, and the aqueous layer was extracted with 3 x 30

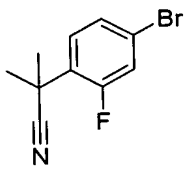
mL 10% MeOH in CH_2Cl_2. The organic layers were combined, and dried over Na_2SO_4. After filtering off the solids, the liquid was concentrated by rotary evaporation to an oil. The oil was flash chromatographed, and the resulting product was further purified by preparatory HPLC. Yield: 28 mg, 5%. ^1H NMR (400MHz, DMSO-d_6): δ 1.25-1.57 (m, 8H), 1.72 (s, 6H), 2.11-2.17 (m, 2H), 2.50-2.56 (m, 8H), 2.63-2.65 (m, 2H), 2.78(d, J = 16 Hz, 1H), 3.71(d, J = 16 Hz, 1H), 3.84 (d, J = 16 Hz, 1H), 7.06 (s, 1H), 7.17-7.23 (m, 2H), 7.36-7.42 (m, 1H), 10.88 (s, 1H). MS (ESI): 530 (M-H).

Step 1: (4-Bromo-2-fluoro-phenyl)-acetonitrile



To a solution of 4-bromo-1-bromomethyl-2-fluoro-benzene (8.15 g, 30.4 mmol) dissolved in DMF (16 mL) were added sodium cyanide (2.24 g, 45.6 mmol) and water (2 mL). The reaction was stirred for one hour at 70 °C. To the reaction was added 130 mL water; 120 mL saturated $NaHCO_3$, and 100 mL EtOAc. The layers were separated, and the aqueous layer was extracted with 3 x 100 mL EtOAc. The combined organics were washed with 100 mL water, and then dried over Na_2SO_4. After filtering off the solids, the mother liquor was concentrated to the desired product by rotary evaporation (6.5 g, 99% yield). MS (APCI): 240 (M+H), 242 (M+2+H).

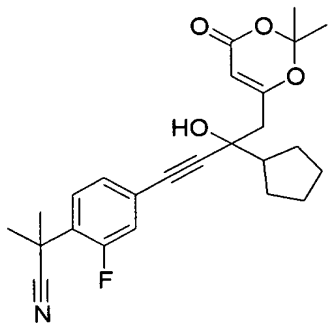
Step 2: 2-(4-Bromo-2-fluoro-phenyl)-2-methyl-propionitrile



To a slurry of sodium hydride (60% dispersion in mineral oil, 0.82 g, 20.6 mmol) in DMF (20 mL) cooled to 0 °C was added a solution of (4-bromo-2-fluoro-phenyl)-acetonitrile

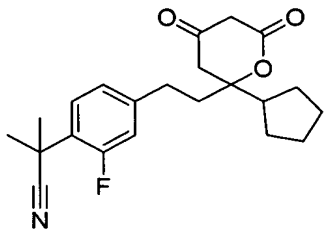
(2.0 g, 9.35 mmol) from Step 1 above, dissolved in THF (10 mL). The reaction was stirred till gas evolution ceased, and then iodomethane (1.3 mL, 20.6 mmol) was added slowly. The reaction was stirred for 30 minutes, and then diluted with 100 mL EtOAc. The solids were removed by filtration, and the organic layer was washed with 100 mL water. The organic layer was dried over $MgSO_4$, and then filtered. The mother liquor was concentrated by rotary evaporation, and the product was distilled under high vacuum (0.3 torr, 45 °C). Yield: 2.25 g, 99%. %. ^{1}H NMR ($CDCl_3$) δ: 2.81 (s, 3H), 2.88 (s, 3H), 7.20 – 7.25 (m, 3H).

Step 3: 2-{4-[3-cyclopentyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxybut-1-ynyl]-2-fluorophenyl}-2-methylpropanenitrile



To a solution of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile (3.0g, 12.4 mmol) in diisopropylamine (32 mL) from step 2 above, and DMF (16 mL) was added racemic 6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3.2 g, 12.4 mmol), $PdCl_2(PPh_3)_2$ (350 mg, 4 mol%), CuI (71 mg, 3 mol%). The mixture was heated to 90 °C for 30 min before it was cooled down to room temperature. The reaction was diluted with aqueous NH_4Cl, extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and evaporated to dryness. The mixture was purified by flash column chromatography (10-50 % EtOAc in hexanes) to give the product (4.2 g, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65-1.76 (m, 14 H), 1.79 (s, 6 H), 1.82-1.85 (m, 1 H), 2.24 (s, 1 H), 2.59 (s, 1 H), 2.67 (m, 2 H), 5.46 (m, 1 H), 7.11 (dd, *J*=12.15, 1.60 Hz, 1 H), 7.18 (dd, *J*=8.10, 1.70 Hz, 1 H), 7.45 (t, *J*=8.10 Hz, 1 H).

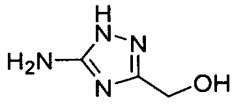
Step 4: 2-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile



To a solution of 2-{4-[3-cyclopentyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxybut-1-ynyl]-2-fluorophenyl}-2-methylpropanenitrile (4.25 g, 10.0 mmol) from step 3 above, in MeOH (100 mL) was added $Pd(OH)_2$ (1.0 g, 20 wt%). The mixture was stirred under H_2 for 12 hours before it was filtered through a pad of celite. The solvent was removed and the residue was taken directly into next step without further purification.

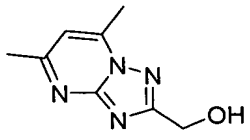
The crude mixture was dissolved in anhydrous MeOH (100 mL) and treated with K_2CO_3 (2.8 g, 10 mmol). The reaction was heated at 45 °C for 40 min before it was cooled down to room temperature. The crude mixture was diluted with aqueous NH_4Cl and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was removed and the mixture was purified by flash column chromatography (EtOAc in hexanes, 10-40 % gradient) to give the desired product (1.4 g, 35% for two steps). ^1H NMR ($CDCl_3$) δ: 1.60-1.73(m, 6 H), 1.92-1.98 (m, 2 H), 2.22-2.30 (m, 1 H), 2.65-2.71 (m, 2 H), 2.75-2.80 (m, 2 H), 6.88-6.96 (m, 2 H), 7.37-7.43 (m, 1 H).

Step 5: (5-Amino-1H-[1,2,4]triazol-3-yl)-methanol



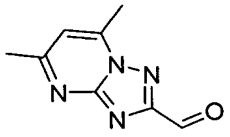
A solution of glycolic acid (70 % in water, 70 mL, 805 mmol) was added to aminoguanidine bicarbonate (55.12 g, 405 mmol) carefully. After foaming subsided, concentrated nitric acid (0.5 mL) was added and the entire reaction was refluxed for 40 hours. The reaction was cooled to 5 °C for 30 minutes, and the solids were filtered. The solids were then triturated with EtOH for 1 hour. The product was then filtered and dried under nitrogen (40.36 g, 52% yield). MS (ESI): 115 (M+H).

Step 6: (5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol



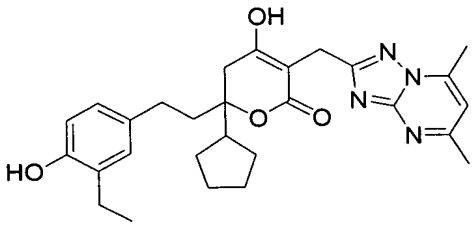
To a slurry of (5-amino-1H-[1,2,4]triazol-3-yl)-methanol (9.5 g, 50 mmol) from Step 5 above in acetic acid (200 mL) was added 2,4-pentanedione (5.13 mL, 50 mmol). The mixture was heated to reflux for 4 hours, and then cooled to room temperature. The product was isolated by removing the solvent by rotary evaporation (8.5 g, 95% yield). MS (ESI): 179 (M+H).

Step 7: 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde



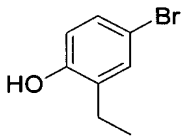
A slurry of 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol (0.3 g, 1.7 mmol) from Step 6 above and IBX (1.4 g, 5.0 mmol) in 1,2-dichloroethane (22 mL) was stirred at 80 °C for 18 hours. The reaction was cooled to room temperature, and diluted with 100 mL CH_2Cl_2. After the solids were removed by filtration, the solvent was removed by rotary evaporation to give a yellow solid. The solid was purified by flash chromatography to give the desired product (229 mg, 77% yield). ^{1}H NMR ($CDCl_3$) δ: 2.72 (s, 3H), 2.86 (s, 3H), 6.96 (s, 1H), 10.24 (s, 1H).

Example 2: 6-Cyclopentyl-3-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-6-[2-(3-ethyl-4-hydroxy-phenyl)-ethyl]-4-hydroxy-5,6-dihydro-pyran-2-one



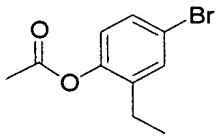
The desired product was prepared analogously to example 1, substituting 6-Cyclopentyl-6-[2-(3-ethyl-4-hydroxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione. from Step 4 below, in place of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile of that example. ^{1}H NMR (DMSO-d_6): δ 0.96 (t, 3H, J = 7.4 Hz), 1.30-1.58 (br m, 8H), 1.95 (m, 2H), 2.41 (m, 12H), 2.63 (d, 1H, J = 17.5 Hz), 3.61 (d, 1H, J = 15.8 Hz), 3.72 (d, 1H, J = 15.8 Hz), 6.52 (d, 1H, J = 8.1 Hz), 6.74 (m, 2H), 6.93 (s, 1H), 8.84 (s, 1H). Anal. Calcd. For $C_{28}H_{34}N_4O_4$•0.5 AcOH: C, 66.90; H, 6.97; N, 10.76. Found: C, 66.89; H, 6.97, N, 10.83.

Step 1: 4-Bromo-2-ethyl-phenol



Sodium hydroxide (1.4g, 35mmol) and hydrazine monohydrate (2.04mL, 42mmol) were added to a solution of 5'-bromo-2'-hydroxyacetophenone (3g, 14mmol) dissolved in triethylene glycol (17mL). The reaction mixture was heated to 170°C for 24 h and then partitioned between 1N HCl and EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over $Na_2SO_4$and concentrated. The residue was purified by flash silica gel chromatography (0% to 10% EtOAc in hexanes) to give the title compound (2.52 g, 90%). ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3H, J = 7.5 Hz), 2.60 (q, 2H, J = 7.5 Hz), 6.64 (d, 1H, J = 8.5 Hz), 7.17 (dd, 1H, J = 8.5, 2.5 Hz), 7.24 (d, 1H, J = 2.5 Hz).

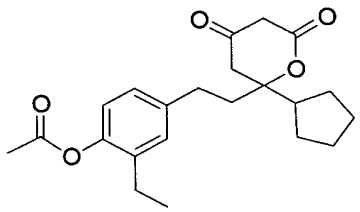
Step 2: Acetic acid 4-bromo-2-ethyl-phenyl ester.



Acetyl chloride (1.06mL, 14.9mmol) followed by triethylamine (2.08mL, 14.9mmol) were added to a cooled 0°C solution of 4-Bromo-2-ethyl-phenol (2.5g, 12.4mmol, from Step 1 above) dissolved in CH_2Cl_2. The reaction was stirred for 2 hrs and then partitioned between 1N HCl and EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to a brown oil. The oil was purified by silica gel chromatography

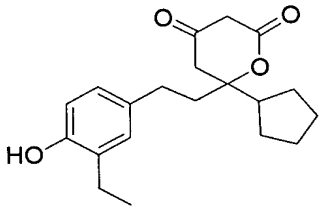
(0% to 10% EtOAc in hexanes) to give the title compound as a clear oil (2.44g, 81%). ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 3H, J = 7.7 Hz), 2.32 (s, 3H), 2.52 (q, 2H, J = 7.7 Hz), 6.89 (d, 1H, J = 8.5 Hz), 7.32 (dd, 1H, J = 8.5, 2.2 Hz), 7.38 (d, 1H, J = 2.2 Hz).

Step 3: Acetic acid 4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-ethyl-phenyl ester.



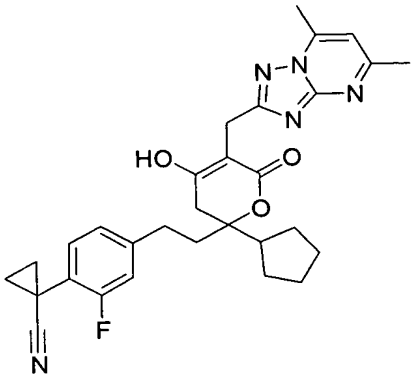
The title compound was prepared analogously to step 3 in Example 1where Acetic acid 4-bromo-2-ethyl-phenyl ester from step 2 above, was substituted in place of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile of that example. ESIMS: MH^+ 373.20, MH^- 371.20

Step 4: 6-Cyclopentyl-6-[2-(3-ethyl-4-hydroxy-phenyl)-ethyl]-dihydro-pyran-2,4-dione.



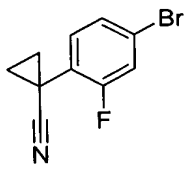
A mixture of acetic acid 4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-ethyl-phenyl ester (0.92g, 2.47mmol), from step 3 above, potassium carbonate (0.68g, 4.9mmol) in MeOH (10mL) was stirred at rt for 1h. The reaction mixture was partitioned between 1N HCl and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to a yellow oil. The oil was purified by silica gel chromatography (20% to 40% EtOAc in hexanes) to give the title compound (2.44g, 59%). ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3H, J = 7.6 Hz), 1.43-1.78 (br m, 8H), 1.87 – 2.01 (m, 2H), 2.28 (m, 1H), 2.57 – 2.63 (m, 4H), 2.76 (s, 2H), 3.42 (s, 2H), 4.63 (s, 1H), 6.68 (d, 1H, J = 8.1 Hz), 6.84 (d, 1H, J = 8.1 Hz), 6.90 (s, 1H). Anal. Calcd. For $C_{20}H_{26}O_4$•0.25 H_2O: C, 71.72; H, 7.98. Found: C, 71.10; H, 7.99.

Example 3: 1-(4-{2-[2-Cyclopentyl-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]-ethyl}-2-fluoro-phenyl)-cyclopropanecarbonitrile



The desired product was prepared analogously to example 1, substituting 1-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-cyclopropanecarbonitrile (0.24 g, 0.65 mmol) from Step 3 below, in place of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile of that example. Yield: 64 mg, 19%. ^{1}H NMR ($CDCl_3$) δ: 1.25 – 1.30 (m, 2H), 1.42 – 1.68 (m, 10H), 1.88 – 1.93 (m, 2H), 2.30 (p, *J* = 8.59 Hz, 1H), 2.44 – 2.73 (m, 10H), 4.05 (d, *J* = 3.03 Hz, 2H), 6.76 – 6.84 (m, 3H), 7.09 – 7.22 (m, 1H).

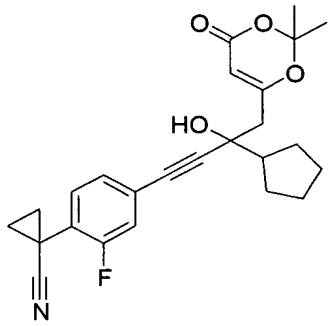
Step 1: 1-(4-Bromo-2-fluoro-phenyl)-cyclopropanecarbonitrile



To a slurry of sodium hydride (60% dispersion in mineral oil, 0.82 g, 20.6 mmol) in DMF (20 mL) cooled to 0 °C was added a solution of (4-bromo-2-fluoro-phenyl)-acetonitrile (2.0 g, 9.35 mmol) prepared in example 1 (step 1), dissolved in THF (10 mL). The reaction was stirred till gas evolution ceased, and then 1,2-dibromoethane (1.8 mL, 20.6 mmol) was added slowly. The reaction was stirred for 30 minutes, and then diluted with 100 mL EtOAc. The solids were removed by filtration, and the organic layer was washed with 100 mL water.

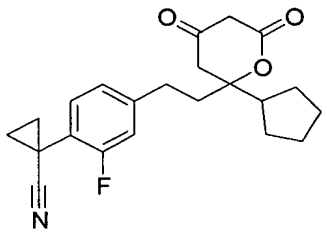
The organic layer was dried over $MgSO_4$, and then filtered. The mother liquor was concentrated by rotary evaporation, and the product was distilled under high vacuum (0.3 torr, 45 °C). Yield: 0.98 g, 44 %. ^{1}H NMR ($CDCl_3$) δ: 1.15 (dd, *J*1 = 5.31 Hz, *J*2 = 2.27 Hz, 2H), 1.48 (dd, *J*1 = 5.05 Hz, *J*2 = 2.53 Hz, 2H), 6.97 – 7.12 (m, 3H).

Step 2: 1-{4-[3-Cyclopentyl-4-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2-fluoro-phenyl}-cyclopropanecarbonitrile



The title compound was prepared analogously to Example 1(step 3), where 1-(4-Bromo-2-fluoro-phenyl)-cyclopropanecarbonitrile from step 1 above, was substituted in place of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile of that example. MS (ESI): 422 (M-H).

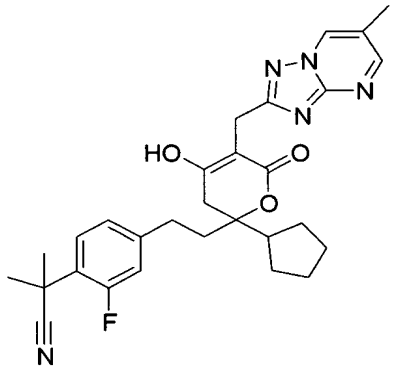
Step 3: 1-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-cyclopropanecarbonitrile



The title compound was prepared analogously to Example 1(step 4)where 1-{4-[3-Cyclopentyl-4-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2-fluoro-phenyl}-cyclopropanecarbonitrile from step 2 above, was substituted in place of 2-{4-[3-cyclopentyl-4-

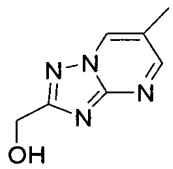
(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxybut-1-ynyl]-2-fluorophenyl}-2-methylpropanenitrile of that example. Yield = 0.367 g, 47%. ^{1}H NMR ($CDCl_3$) δ: 1.27 – 1.30 (m, 2H), 1.51 – 1.73 (m, 10H), 1.84 – 1.89 (m, 2H), 2.19 (p, *J* = 8.08 Hz, 1H), 2.58 – 2.71 (m, 4H), 3.36 (d, *J* = 4.04 Hz, 2H), 6.81 – 6.86 (m, 2H), 7.16 – 7.18 (m, 1H). MS (ESI): 368 (M-H).

Example 4: 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to Example 1 where 6-Methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde from step 2 below was substituted in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde in the final step of that example. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 – 1.71 (m, 8H), 1.76 (s, 6H), 2.00 (m, 2H), 2.06 (s, 1H), 2.10 (s, 1H), 2.38 (m, 1H), 2.39 (s, 3H), 2.68 (m, 2H), 2.81(m, 1H), 4.09 (s, 2H), 6.86 (d, *J* = 12.9 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 7.84 (t, *J* = 8.1Hz, 1H), 8.63 (s, 1H), 8.70 (s, 1H). MS (ESI): 518.6($M+H^+$).

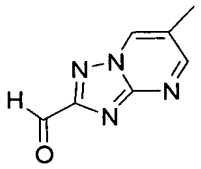
Step 1: Preparation of (6-methyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methanol



To a solution of (3-amino-1*H*-1,2,4-triazol-5-yl)methanol (16.6 g, 87.6 mmol) in acetic acid was added 3-ethoxymethacrolein (10.0 g, 87.6 mmol), and the mixture was heated to 80 °C

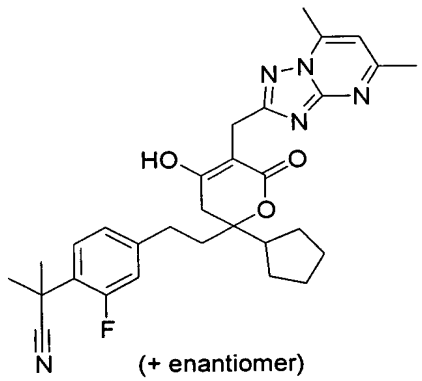
for 4 hours. Upon cooling of the reaction, the product crystallized out of solution. The collected product was a white solid (14.0 g, 92%). ^{1}H NMR (300 MHz, DMSO-D6) δ: 2.38 (m, 3 H) 4.63 (m, 2 H) 5.52 (m, 1 H) 8.75 (m, 1 H) 9.21 (m, 1 H). MS (APCI, M+H$^+$): 163.1, 165.1.

Step 2: Preparation of 6-methyl [1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde



A mixture of (6-methyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methanol(15.7 g, 95.6 mmol) from step 1 above, TEMPO (1.12 mg, 7.2 mmol), and iodobenzene diacetate (33.9 g, 105.2 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 2 hours. Once the reaction was deemed complete, methyl-tert-butyl ether (50 mL) was added slowly to precipitate the product. The concentrated mother liquor was introduced into a silica gel column and eluted with 2% MeOH/CH_2Cl_2 to give additional amount of the aldehyde product as a while solid (12 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.54 (m, 3 H), 8.73 (m, 1 H), 8.85 (m, 1 H), 10.23 (m, 1 H). MS (APCI, M+H$^+$): 163.1.

Example 5: (+)-2-(4-{2-[2-Cyclopentyl-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]-ethyl}-2-fluoro-phenyl)-2-methyl-propionitrile



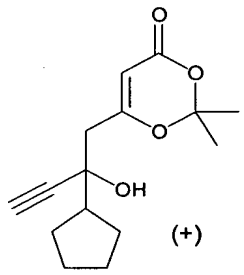
(+ enantiomer)

The desired product was prepared analogously to example 1, substituting (+)-2-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile

from Step 2 below, in place of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile of that example. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.25-1.57 (m, 8H), 1.72 (s, 6H), 2.11-2.17 (m, 2H), 2.50-2.56 (m, 8H), 2.63-2.65 (m, 2H), 2.78(d, *J* = 16 Hz, 1H), 3.71(d, *J* = 16 Hz, 1H), 3.84 (d, *J* = 16 Hz, 1H), 7.06 (s, 1H), 7.17-7.23 (m, 2H), 7.36-7.42 (m, 1H), 10.88 (s, 1H). Anal. Calcd. For $C_{30}H_{36}FN_5O_3 \cdot 1.0\ H_2O$: C, 65.56; H, 6.60; N, 12.74. Found: C, 65.50; H, 6.41; N, 12.61. MS(ESI): 532 $(M+H)^+$.

The desired compound can also be separated from racemic 2-(4-{2-[2-Cyclopentyl-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]-ethyl}-2-fluoro-phenyl)-2-methyl-propionitrile . (100 mg) using chiral HPLC (Chiralpak AS-RH, 150 x 4.6 mm, 0.6 mL/min, 50% CAN, 50% H_2O, 30 °C). (40 mg, 80 % recovery, 14.743 min retention time).

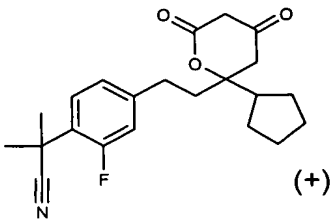
Step 1: Preparation of compound (+)-6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one



(+)

To the optically pure (+)-1-cyclopentyl-1-[(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)methyl]prop-2-ynyl ethyl oxalate from Example 42 (step 2), (2.5 g, 15.1 mmol) in 50 ml of MeOH was added K_2CO_3 (2.0 g). The mixture was stirred at 23 °C for 8h. After complete conversion, the mixture was neutralized with 1N HCl at cold temperature. The aqueous solution was extracted with MTBE (x3) and the organic layer was washed with brine and dry over $MgSO_4$. After removal of MTBE, 1.75 g of the desired product (+ enantiomer) was produced with 95.5% ee and 96% yield.

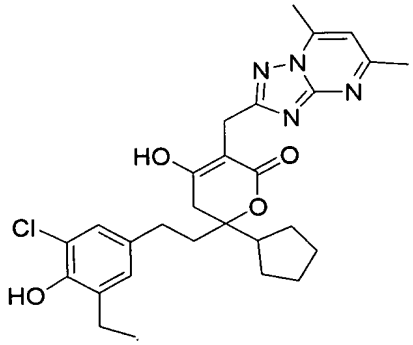
Step 2: (+)-2-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile.



(+)

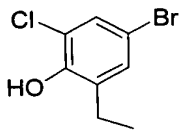
The title compound was prepared analogously to Example 1 (step 4) where (+)-6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one from step 1 above, was substituted in place of racemic 6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one in step 3 of that example. ^{1}H NMR ($CDCl_3$) δ: 1.60-1.73(m, 6 H), 1.92-1.98 (m, 2 H), 2.22-2.30 (m, 1 H), 2.65-2.71 (m, 2 H), 2.75-2.80 (m, 2 H), 6.88-6.96 (m, 2 H), 7.37-7.43 (m, 1 H). MS(ESI):372 $(M+H)^+$.

Example 6: 6-[2-(3-chloro-5-ethyl-4-hydroxyphenyl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one



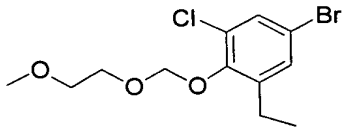
The desired product was prepared analogously to example 1, substituting 6-[2-(3-Chloro-5-ethyl-4-hydroxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione from Step 5 below, in place of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile of that example. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.12 (t, *J*=7.3 Hz, 3 H), 1.46-1.75(m, 8 H), 2.14 (m, 2H), 2.44-2.64 (m, 12 H), 2.83 (d, *J*=17.4 Hz, 1 H), 3.78 (d, *J*=16.2 Hz, 1 H), 3.88 (d, *J*=16.2 Hz, 1 H), 6.94 (s, 1 H), 7.05 (s, 1 H), 7.10 (s, 1 H), 6.86 (s, 1 H), 10.90 (s, 1 H). Anal. Calcd. For $C_{28}H_{33}N_4O_4Cl.H_2O$: C, 61.93; H, 6.50; N 10.32. Found: C, 62.02; H, 6.29; N, 10.13.

Step 1: Preparation of compound 4-Bromo-2-chloro-6-ethyl-phenol.



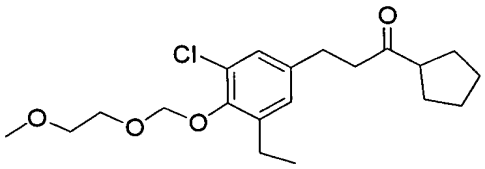
Sodium hydroxide (1.2g, 30mmol) and hydrazine monohydrate (1.75mL, 36mmol) were added to a solution of 5'-bromo-3'-chloro-2'-hydroxyacetophenone (3g, 12mmol) dissolved in triethylene glycol (15mL). The reaction mixture was heated to 160°C for 72 hours and then partitioned between 1N HCl and EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over $Na_2SO_4$and concentrated. The residue was purified by flash silica gel chromatography (0% to 10% EtOAc in hexanes) to give the title compound (2.34 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, *J*=7.6 Hz, 3 H), 2.65 (q, *J*=7.6 Hz, 2 H), 5.55 (s, 1 H), 7.17 (s, 1 H), 7.31 (s, 1 H).

Step 2: Preparation of compound 5-Bromo-1-chloro-3-ethyl-2-(2-methoxy-ethoxymethoxy)-benzene.



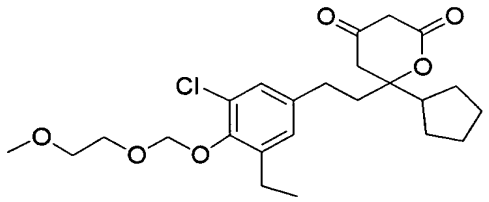
A solution of 4-Bromo-2-chloro-6-ethyl-phenol (2.3g, 9.8mmol) dissolved in THF (10mL) was added to a cooled 0°C suspension of NaH (0.43 g, 10.8 mmol, 60% dispersion in mineral oil) in THF (20ml). After the addition was complete the reaction mixture was warmed up to room temperature and stirred for 30 mins. 2-Methoxyethoxymethyl chloride (1.34mL, 11.7mmol) was added and the reaction was stirred for 15 hours. The reaction mixture was quenched with 1N HCl and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a yellow oil. Purification by flash column chromatography (0% to 10% EtOAc in hexanes) gave the title compound as a clear oil (2.4g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J*=7.3 Hz, 3 H), 2.70 (q, *J*=7.6 Hz, 2 H), 3.40 (s, 3 H), 3.61 (m, 2 H), 3.98 (m, 2 H), 5.15 (s, 2 H), 7.24 (s, 1 H), 7.37 (s, 1 H).

Step 3: 3-[3-Chloro-5-ethyl-4-(2-methoxy-ethoxymethoxy)-phenyl]-1-cyclopentyl-propan-1-one.



A mixture of 5-Bromo-1-chloro-3-ethyl-2-(2-methoxy-ethoxymethoxy)-benzene (1.2g, 3.6mmol), 1-Cyclopentyl-2-propen-1-ol (0.5g, 10.4mmol), palladium (II) acetate (0.5 mg, 0.05 mol %), and sodium acetate (0.32 g, 4.0 mmol) in N-methylpyrrolidinone (7mL) was heated to 125°C under N_2 for 4h. The reaction mixture was partitioned between 1N HCl and EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to a black oil. The oil was purified by flash column chromatography (0% to 5% EtOAc in hexanes) to give the desired product (0.76g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J*=7.6 Hz, 3 H), 1.54-1.81 (m, 8 H), 2.68 (q, *J*=7.6 Hz, 2 H), 2.73 (m, 2 H), 2.79-2.85 (m, 3 H), 3.40 (s, 3 H), 3.61 (m, 2 H), 3.98 (m, 2 H), 5.14 (s, 2 H), 6.90 (d, *J*=2.0 Hz, 1 H), 7.03 (d, *J*=2.0 Hz, 1 H).

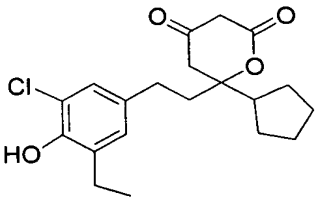
Step 4: 6-{2-[3-Chloro-5-ethyl-4-(2-methoxy-ethoxymethoxy)-phenyl]-ethyl}-6-cyclopentyl-dihydro-pyran-2,4-dione.



Methyl acetoacetate (0.67 mL, 6.2mmol) was added to a cooled 0 °C suspension of NaH (0.25 g, 6.2 mmol, 60% dispersion in mineral oil) in THF (5ml). After 30 min n-BuLi (3.86mL, 6.2mmol, 1.6M in hexanes) was added. The resulting dianion was stirred for an additional 30 min and then treated with a solution of 3-[3-Chloro-5-ethyl-4-(2-methoxy-ethoxymethoxy)-phenyl]-1-cyclopentyl-propan-1-one (0.76g, 2.1 mmol) in THF (2ml). After stirring for 4h at 0°C, the reaction mixture was quenched with 1N HCl and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a yellow oil that was used without further purification.

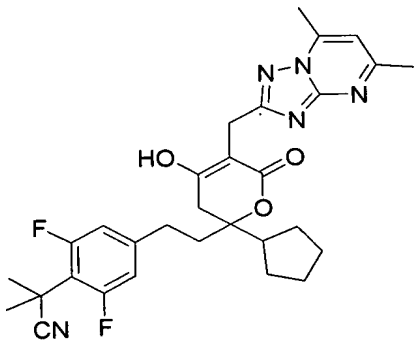
The oil was dissolved in methanol (10mL), treated with potassium carbonate (0.85g, 6.2 mmol), and refluxed under N_2 for 2h. The reaction mixture was partitioned between 1N HCl and EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a yellow oil that was purified by silica gel chromatography (0% to 30% EtOAc in hexanes) to give the title compound as a gum (0.22g, 24% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J*=7.6 Hz, 3 H), 1.32-180 (br m, 8 H), 1.92 (m, 2 H), 2.26 (m, 1 H), 2.59 (m, 2 H), 2.69 (q, *J*=7.6 Hz, 2 H), 2.76 (s, 2 H), 3.40 (s, 3 H), 3.43 (s, 2 H), 3.61 (m, 2 H), 3.98 (m, 2 H), 5.14 (s, 2 H), 6.86 (s, 1 H), 7.00 (s, 1 H).

Step 5: 6-[2-(3-Chloro-5-ethyl-4-hydroxy-phenyl)-ethyl]-6-cyclopentyl-dihydro-pyran-2,4-dione.



Trifluoroacetic acid (0.07mL, 0.88mmol) was added to a solution of 6-{2-[3-Chloro-5-ethyl-4-(2-methoxy-ethoxymethoxy)-phenyl]-ethyl}-6-cyclopentyl-dihydro-pyran-2,4-dione (0.2g, 0.44mmol) dissolved in CH_2Cl_2 (4mL). The reaction mixture was stirred for 2 hours at room temperature and then partitioned between H_2O and EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to an oil. The oil was purified by flash column chromatography (0% to 30% EtOAc in hexanes) to give the title compound as a solid. (0.12g, 75%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J*=7.6 Hz, 3 H), 1.58-173 (br m, 8 H), 1.92 (m, 2 H), 2.26 (m, 1 H), 2.57 (m, 2 H), 2.65 (q, *J*=7.6 Hz, 2 H), 2.76 (s, 2 H), 3.43 (s, 2 H), 5.47 (s, 1 H), 6.81 (s, 1 H), 6.95 (s, 1 H). MS: $C_{20}H_{24}O_4Cl$ (M - H) 363.10.

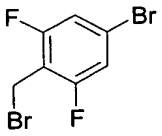
Example 7: 2-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile



A solution of 2-{4-[2-(2-Cyclopentyl-4, 6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2,6-difluoro-phenyl}-2-methyl-propionitrile (389 mg, 1.0 mmol) from step 5 below in anhydrous MeOH (4.0 mL) was treated with 5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde (76.6 mg, 1.30 mmol), followed by borane-dimethylamine complex at room temperature. The reaction was stirred for 12 hours before it was quenched by the addition of 1 N HCl. The

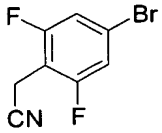
mixture was extracted with 10% MeOH in CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was removed and the residue was purified by flash column chromatography (80% EtOAc, 14% Hexane, 6% MeOH and 0.5% acetic acid) to give the product (192 mg, 35% yield). ^{1}H NMR ($CDCl_3$) δ: 1.52 – 1.75 (m, 6 H), 1.83 (s, 3 H), 1.93 - 1.99 (m, 3 H), 2.09 (s, 3 H), 2.36 (m, 1 H), 2.45 (d, *J*=17.94 Hz, 2 H), 2.60 – 2.64 (m, 2 H), 2.66 (s, 3 H), 2.72 (d, *J*=6.06 Hz, 1 H), 2.78 (d, *J*=7.33 Hz, 1 H), 2.79 (s, 3 H), 4.08 (s, 2 H), 6.68 (d, *J*=10.86 Hz, 2 H), 6.85 (s, 1 H). MS (ESI): 548 (M-H).

Step 1: 5-Bromo-2-bromomethyl-1, 3-difluoro-benzene



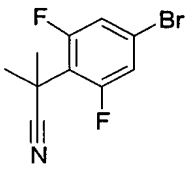
A solution of 5-Bromo-2-hydroxymethyl-1,3-difluoro-benzene (0.89g, 4.0 mmol) and 30 wt% of hydrogen bromide in acetic acid was stirred at room temperature for 90 minutes before it was poured into 80 ml of water. The mixture was extracted with pentane (3 X 50 ml) and the combined organic layers were washed with water (3 X 20 ml), dried over $MgSO_4$ and concentrated at low pressure to afford the desired product (10.0 g, 98% yield). ^{1}H NMR ($CDCl_3$) δ: 4.47 (s, 2H), 7.09-7.10 (m, 1H), 7.12- 7.13 (m, 1H).

Step 2: (4-Bromo-2, 6-difluoro-phenyl)-acetonitrile



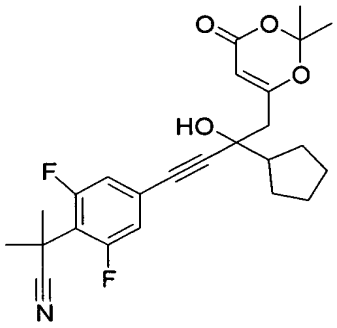
The desired product was prepared analogously to step 1 in Example 1, substituting 5-Bromo-2-bromomethyl-1, 3-difluoro-benzene from step 1 above in place of 4-bromo-1-bromomethyl-2-fluoro-benzene of that example. ^{1}H NMR ($CDCl_3$) δ: 3.59 (s, 2H), 7.18 (d, *J*=6.6 Hz, 2 H).

Step 3: 2-(4-Bromo-2, 6-difluoro-phenyl)-2-methyl-propionitrile



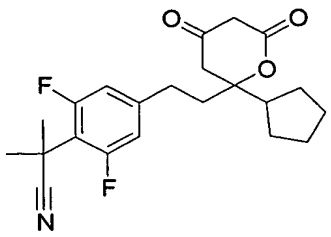
The desired product was prepared analogously to step 2 in Example 1, substituting (4-Bromo-2,6-difluoro-phenyl)-acetonitrile from step 2 above, in place of (4-bromo-2-fluoro-phenyl)-acetonitrile of that example. ^{1}H NMR ($CDCl_3$) δ: 1.87 (s, 6H), 7.13 (d, *J*=9.3 Hz, 2 H).

Step 4: 2-{4-[3-Cyclopentyl-4-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2,6-difluoro-phenyl}-2-methyl-propionitrile



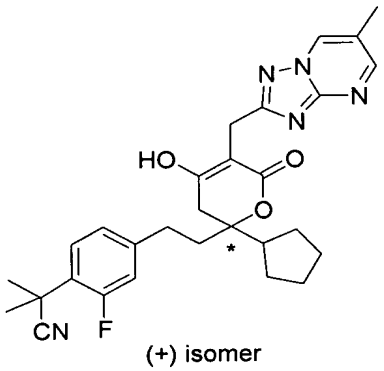
The title compound was prepared analogously to Example 1(step 3), where 2-(4-Bromo-2,6-difluoro-phenyl)-2-methyl-propionitrile from step 3 above was substituted in place of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile in that example. ^{1}H NMR ($CDCl_3$) δ: 1.38 – 1.48 (m, 4 H), 1.57 – 1.77 (m, 5 H), 1.85 (s, 6 H), 1.92 (t, *J*=8.6 Hz, 2 H), 2.25 (m, 1 H), 2.65 (dd, *J*=15.9, 7.6 Hz, 2 H), 2.75 (dd, *J*=28.8, 15.7 Hz, 2 H), 3.43 (d, *J*=4.6 Hz, 2 H), 6.71 (d, *J*=10.9 Hz, 1 H). MS (ESI): 442 (M-H).

Step 5: 2-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2,6-difluoro-phenyl}-2-methyl-propionitrile



The title compound was prepared analogously to Example 1 (step 4) where 2-{4-[3-Cyclopentyl-4-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2,6-difluoro-phenyl}-2-methyl-propionitrile from step 4 above, was substituted in place of 2-{4-[3-cyclopentyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxybut-1-ynyl]-2-fluorophenyl}-2-methylpropanenitrile of that example. Yield = 0.367 g, 47%. ^{1}H NMR ($CDCl_3$) δ: 1.27 – 1.30 (m, 2H), 1.51 – 1.73 (m, 10H), 1.84 – 1.89 (m, 2H), 2.19 (p, *J* = 8.08 Hz, 1H), 2.58 – 2.71 (m, 4H), 3.36 (d, *J* = 4.04 Hz, 2H), 6.81 – 6.86 (m, 2H), 7.16 – 7.18 (m, 1H). MS (ESI): 368 (M-H).

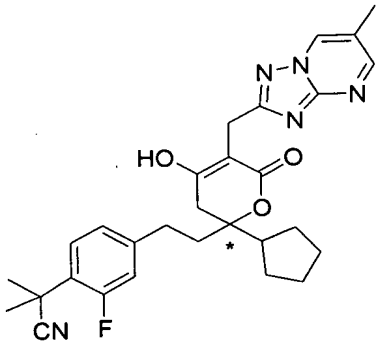
Example 8: 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



(+) isomer

The title compound was isolated by chiral chromatography of racemic material described in Example 4: Conditions: Chiralpak AS-RH, 150 x 4.6 mm, 0.6 mL/min, 30 °C; 40% acetonitrile, 60% water, 0.1% formic acid; retention time 24.5 min.

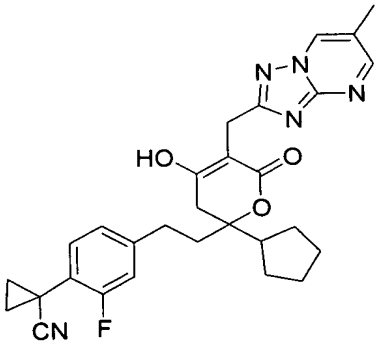
Example 9: 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



(-) isomer

The title compound was isolated by chiral chromatography of racemic material described in Example 4. Conditions: Chiralpak AS-RH, 150 x 4.6 mm, 0.6 mL/min, 30 °C; 40% acetonitrile, 60% water, 0.1% formic acid; retention time 17.99 min.

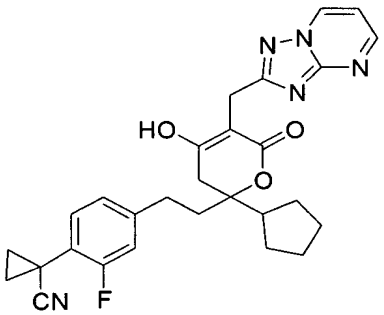
Example 10: 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile



A solution of 1-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-cyclopropanecarbonitrile (568 mg, 1.54 mmol) from step 3 in example 3, in anhydrous MeOH (6.0 mL) was treated with 6-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (324 mg, 2.0 mmol), (prepared in step 2, example 4), followed by borane-dimethylamine complex (118 mg, 2.0 mmol) at room temperature. The reaction was stirred for 1 hour before it was cooled to –10 °C for 2 hours. The precipitate was removed by filtration, and the filtrate was concentrated to an oil. The oil was purified by flash chromatography (50g SiO_2, 1:3 -> 1:0 (93.5% ethyl acetate, 6% methanol, 0.5% acetic acid) : (81.5% hexanes, 12% ethyl acetate, 6% methanol, 0.5% acetic acid)) to give the desired product as an oil. It was further purified by crystallization from ethyl acetate / hexanes to give a white powder (146 mg, 18%). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.41–1.64 (m, 8 H), 1.84-1.88 (m, 2 H), 2.22-2.28 (m, 2 H), 2.42 (s,

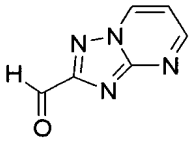
3 H), 2.49-2.59 (m, 4 H), 2.65-2.74 (m, 3 H), 3.97-4.05 (m, 2 H), 6.72-6.82 (m, 2 H), 7.05-7.10 (m, 1 H), 8.55 (s, 1 H), 8.67 (s, 1 H).

Example 11: 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile



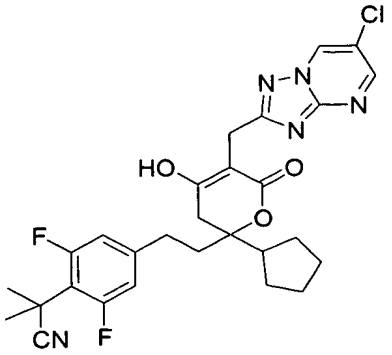
A solution of 1-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-cyclopropanecarbonitrile (568 mg, 1.54 mmol) from step 3 in example 3, in anhydrous MeOH (6.0 mL) was treated with [1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (296 mg, 2.0 mmol), from step 1 below, followed by borane-dimethylamine complex (118 mg, 2.0 mmol) at room temperature. The reaction was stirred for 1 hour and then was concentrated to an oil. The oil was purified by flash chromatography (50g SiO_2, 70% ethyl acetate, 6% methanol, 0.5% acetic acid, 23.5% hexanes) to give the desired product as an oil. It was further purified by crystallization from ethyl acetate / hexanes to give a white powder (142 mg, 18%). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.11-1.18 (m, 2 H), 1.31-1.52 (m, 10 H), 1.75-1.80 (m, 2 H), 2.16 (t, *J*=8.84 Hz, 1 H), 2.34 (d, *J*=17.68 Hz, 1 H), 2.46 (t, *J*=7.83 Hz, 2 H), 2.59 (d, *J*=17.94 Hz, 1 H), 3.94 (d, *J*=3.79 Hz, 2 H), 6.62-6.70 (m, 2 H), 6.97 (t, *J*=7.83 Hz, 1 H), 7.02-7.04 (m, 1 H), 6.82-6.85 (m, 2 H).

Step 1: Preparation of 6-methyl [1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde



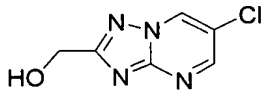
The desired product was prepared analogously to step 4 in Example 7 substituting 3-methoxy acrolein, in place of 3-ethoxymethacrolein of that example.

Example 12: 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile



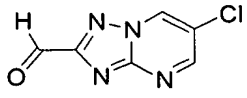
The desired product was prepared analogously to Example 7 substituting 6-Chloro-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde, from step 2 below, in place of 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde of that example. ^{1}H NMR ($CDCl_3$) δ: 1.57 – 1.71 (m, 4 H), 1.83 (s, 6 H), 1.94 – 2.00 (m, 3 H), 2.33 - 2.40 (m, 2 H), 2.46 (d, *J*=17.68 Hz, 1 H), 2.65 (t, *J*=9.09 Hz, 2 H), 2.75 (d, *J*=18.19 Hz, 2 H), 3.42 (d, *J*=2.02 Hz, 1 H), 3.75 (t, *J*=9.35 Hz, 1 H), 4.11 (s, 2 H), 6.68 (d, *J*=10.86 Hz, 2 H), 8.78 (d, *J*=2.53 Hz, 1 H), 8.87 (d, *J*=2.53 Hz, 1 H). MS (ESI): 555 (M-H).

Step 1: Preparation of compound (6-chloro[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methanol



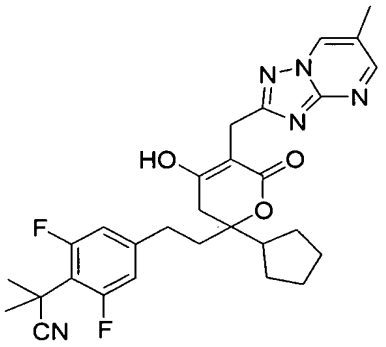
To a slurry of (3-amino-1*H*-1,2,4-triazol-5-yl)methanol (28.5 g, 150 mmol) in acetic acid was added chloromalonaldehyde (16 g, 150 mmol). The mixture was heated to 80 °C for 4 hours. Upon cooling of the reaction to room temperature, the product crystallized out as a white solid (25.5 g, 92%). ^{1}H NMR (300 MHz, DMSO-D6) δ: 4.67 (s, 2 H), 5.62 (s, 1 H), 8.94 (d, *J*=2.45 Hz, 1 H), 9.81 (d, *J*=2.45 Hz, 1 H). MS (APCI): 185.0 ($M+H^+$).

Step 2: 6-chloro[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde



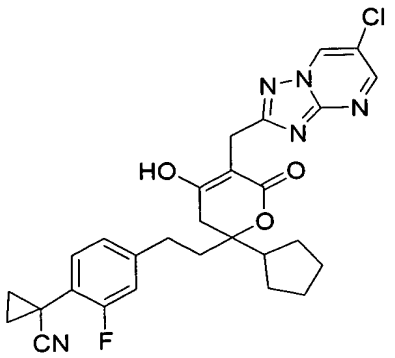
A mixture of (6-chloro[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methanol (9.86 g, 53.4 mmol), TEMPO (626 mg, 4.01 mmol), iodobenzene diacetate (18.9 g, 58.76 mmol) in CH_2Cl_2 (75 mL) was stirred at room temperature for 2 hours. Once the reaction was deemed complete, methyl-tert-butyl ether (50 mL) was added slowly to precipitate the product. as a while solid (8.72 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.93 (d, *J*=2.45 Hz, 1 H), 8.99 (d, *J*=2.64 Hz, 1 H), 10.25 (s, 1 H). MS (APCI): 183.0, 185.0 ($M+H^+$).

Example 13: 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile



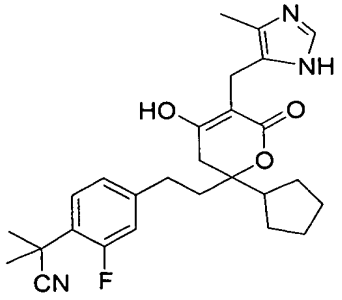
The desired product was prepared analogously to Example 7, substituting 6-Methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (prepared in step 2, example 4) in place of 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde of that example. ^{1}H NMR ($CDCl_3$) δ: 1.34 – 1.40 (m, 2 H), 1.60 – 1.73 (m, 4 H), 1.83 (s, 6 H), 1.83 – 1.86 (m, 3 H), 1.93 – 1.99 (m, 2 H), 2.37 (m, 1 H), 2.42 (d, *J*=5.56 Hz, 1 H), 2.48 (s, 3 H), 2.64 (t, *J*=8.34 Hz, 2 H), 2.75 (d, *J*=17.94 Hz, 1 H), 4.09 (s, 2 H), 6.67 (d, *J*=11.12 Hz, 2 H), 8.61 (d, *J*=1.26 Hz, 1 H), 8.69 (d, *J*=2.27 Hz, 1 H). MS (ESI): 534 (M-H).

Example 14: 1-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile



A solution of 1-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-cyclopropanecarbonitrile (568 mg, 1.54 mmol) from step 3 in example 3 in anhydrous MeOH (6.0 mL) was treated with 6-chloro-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (365 mg, 2.0 mmol), prepared in 2 from example 12, followed by borane-dimethylamine complex (118 mg, 2.0 mmol) at room temperature. The reaction was stirred for 1 hour and then was concentrated to an oil. The oil was purified by flash chromatography (50g SiO_2, 70% ethyl acetate, 6% methanol, 0.5% acetic acid, 23.5% hexanes). The resultant oil was further purified by flash 50g SiO_2, 1:3 -> 1:0 (93.5% ethyl acetate, 6% methanol, 0.5% acetic acid): (81.5% hexanes, 12% ethyl acetate, 6% methanol, 0.5% acetic acid) to give the desired product as an oil. It was further purified by crystallization from ethyl acetate / hexanes to give a white powder (48.6 mg, 6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19-1.24 (m, 2 H), 1.39-1.61 (m, 10 H), 1.83-1.87 (m, 2 H), 2.25 (t, *J*=8.59 Hz, 1 H), 2.38 (d, *J*=17.94 Hz, 1 H), 2.54 (t, *J*=7.71 Hz, 2 H), 2.64 (d, *J*=17.94 Hz, 1 H), 3.98 (d, *J*=5.56 Hz, 2 H), 6.71-6.77 (m, 2 H), 7.06 (t, *J*=7.83 Hz, 1 H), 8.66 (s, 1 H), 8.73 (s, 1 H).

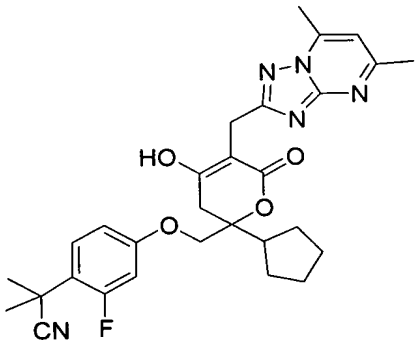
Example 15: 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(4-methyl-1H-imidazol-5-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



The title compound was prepared analogously to Example 1 where 5-Methyl-3H-imidazole-4-carbaldehyde was substituted in place of 5,7-Dimethyl-[1,2,4]triazolo[1,5-

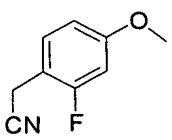
a]pyrimidine-2-carbaldehyde in that example. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 – 1.71 (m, 8H), 1.70 (s, 6H), 1.88 (m, 2H), 2.12 (s, 3H), 2.28 (m, 1H), 2.43 (d, *J* = 103, 17.4 Hz, 1H), 2.50 (m, 2H), 2.58 (m, 3H), 7.02 (d, *J* = 6.57 Hz, 1H), 7.11 (d, *J* = 13.1 Hz, 1H), 7.34 (t, *J* = 8.6Hz, 1H), 7.78 (s, 1H). MS (ESI): 467.1 ($M+H^+$).

Example 16: 2-[4-({2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile



A solution of 2-[4-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-ylmethoxy)-2-fluoro-phenyl]-2-methyl-propionitrile (200 mg, 0.54 mmol) from step 5 below, in anhydrous MeOH (4.0 mL) was treated with 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (150 mg, 0.86 mmol), followed by borane-dimethylamine complex (47 mg, 0.8 mmol) at room temperature. The reaction was stirred for 5 hours before it was quenched by the addition of 0.5N HCl (25 mL). The mixture was extracted with 10% MeOH in CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by crystallization from EtOAc/Hexanes to give the product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.64 (m, 8 H), 1.70 (s, 6 H), 2.50 (1, 1 H), 2.57 (s, 3 H), 2.63 (s, 3 H), 2.79 (m, 2 H), 3.77 (m, 2 H), 4.12 (brs, 1 H), 4.50 (m, 1 H), 6.95 (m 3 H), 7.35 (m, 1 H), 10.95 (brs, 1 H).

Step 1: Preparation of compound (2-Fluoro-4-methoxy-phenyl)-acetonitrile

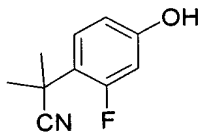


To a mixture of 1-Bromomethyl-2-fluoro-4-methoxy-benzene (4.5 g, 21 mmol) and Tetrabutylammonium iodide (0.66 g, 2.1 mmol) in CH_2Cl_2 (50 mL) was added a solution potassium cyanide (4.0 g, 60 mmol) in water (50 mL). The resulting biphasic mixture was stirred vigorously for 8 hours. The reaction was poured into water (100 mL) and extracted with CH_2Cl_2 (2X 50 mL). The organics were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (10-30 % EtOAc in hexanes) to give the product (2.6 g, 75% yield) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.66 (s, 2 H), 3.82 (s, 3 H), 6.69 (m, 2 H), 7.31 (m, 1 H).

Step 2: Preparation of compound 2-(2-Fluoro-4-methoxy-phenyl)-2-methyl-propionitrile

A solution of (2-Fluoro-4-methoxy-phenyl)-acetonitrile, from step 1 above, (5 g, 30 mmol) and Iodomethane (6.03 mL, 97 mmol) in DMSO (30 mL) was added drop wise over 2 hours to a stirring solution of KOH (7.47 g, 133 mmol) in water (4 mL) and DMSO (20 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 4 hours. The reaction was poured into water (100 mL) and extracted with EtOAc (2X 50 mL). The organics were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (0-10 % EtOAc in hexanes) to give the product (4.76 g, 82% yield) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.82 (s, 6 H), 3.85 (s, 3 H), 6.64 (d, *J*=9.6 Hz, 2 H), 7.42 (m, 1 H).

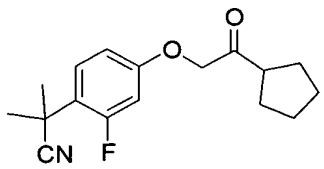
Step 3: Preparation of compound 2-(2-Fluoro-4-hydroxy-phenyl)-2-methyl-propionitrile



To a solution of 2-(2-Fluoro-4-methoxy-phenyl)-2-methyl-propionitrile, from step 2 above, (1.5 g, 7.8 mmol) in CH_2Cl_2 (75 mL) at –78 °C was added Boron tribromide (1M solution in CH_2Cl_2) (16 mL, 16 mmol). The solution was allowed to warm to room temperature and stir for 48 hours. The reaction was quenched with 0.5N HCl (50 mL) and poured into

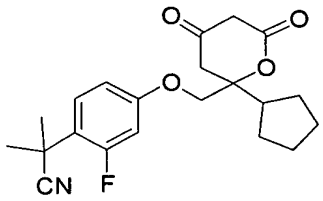
water (100 mL). The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (50mL). The combined organics were washed with water (100 mL), dried over Na_2SO_4, filtered and concentrated. The resulting oil was used without further purification.

Step 4: Preparation of compound 2-[4-(2-Cyclopentyl-2-oxo-ethoxy)-2-fluoro-phenyl]-2-methyl-propionitrile



Potassium carbonate (3.1 g, 22 mmol) was added to a solution of 2-(2-Fluoro-4-hydroxy-phenyl)-2-methyl-propionitrile, from step 3 above, (1.0 g, 6.0 mmol) and 2-Chloro-1-cyclopentyl-ethanone (3.3 g, 22 mmol) in DMF (20 mL). The mixture was stirred at room temperature for 16 hours. The mixture was poured into water (100 mL) and extracted with EtOAc (2X 50 mL). The organics were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (0-15 % EtOAc in hexanes) to give the product (1.2 g, 75% yield) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.57-1.93 (m, 14 H), 3.10 (m, 1 H), 4.64 (s, 2 H), 6.65 (d, *J*=9.6 Hz, 2 H), 7.37 (t, *J*=8.9 Hz, 1 H).

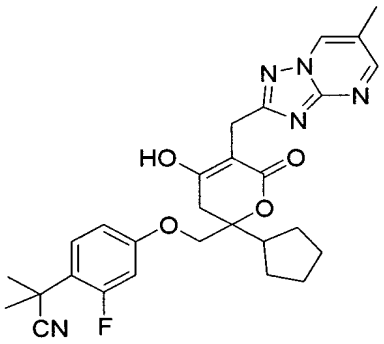
Step 5: 2-[4-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-ylmethoxy)-2-fluoro-phenyl]-2-methyl-propionitrile



Sodium hydride (60%) (0.49 g, 12.3 mmol) was magnetically stirred in dry THF (33 mL) and cooled to 0 °C. The mixture was then treated with Methyl acetoacetate (1.34 mL, 12.3 mmol) drop wise over 15 min. The reaction was allowed to stir for 30 min at 0 °C. To the resulting clear solution was added nBuLi (1.6M in Hexanes) (7.71 mL, 12.3 mmol). The

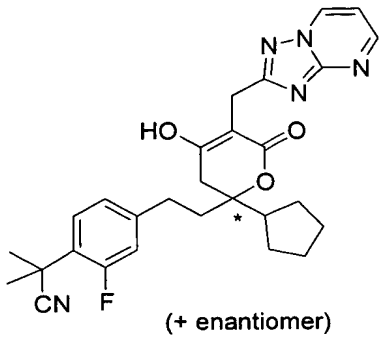
reaction was then allowed to stir for 30 min at 0 °C. To the yellow solution was added 2-[4-(2-Cyclopentyl-2-oxo-ethoxy)-2-fluoro-phenyl]-2-methyl-propionitrile, from step 4 above, (1.19g, 4.1 mmol) as a solution in dry THF (15 mL). The result was stirred at 0 °C for 15 min and then at room temperature for 90 min. The solution was next poured into 0.5N HCl (100 mL) and extracted with EtOAc (2X 50 mL). The organics were concentrated and the residue dissolved in MeOH (33 mL) and treated with K_2CO_3 (1.5 g). The mixture was heated to 65 °C and maintained for 1 hr. The reaction was cooled and poured into 0.5N HCl (100 mL) and extracted with EtOAc (2X 50 mL). The organics were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel) eluting with CH_2Cl_2 through 1% MeOH in CH_2Cl_2 to yield the title compound as a white solid (1.21g, 79%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.55 (m, 8 H), 1.69 (s, 6 H), 2.37 (m, 1 H), 2.62 (s, 2 H), 3.33 (s, 2 H), 4.10 (m, 2 H), 6.87 (m 2 H), 7.34 (m 1 H).

Example 17: 2-[4-({2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}methoxy)-2-fluorophenyl]-2-methylpropanenitrile



A solution of 2-[4-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-ylmethoxy)-2-fluoro-phenyl]-2-methyl-propionitrile from example 16 (step 5), (200 mg, 0.54 mmol) in anhydrous MeOH (4.0 mL) was treated with 6-Methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (140 mg, 0.86 mmol), prepared in example 4 (step 2), followed by borane-dimethylamine complex (47 mg, 0.8 mmol) at room temperature. The reaction was stirred for 5 hours before it was quenched by the addition of 0.5N HCl (25 mL). The mixture was extracted with 10% MeOH in CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by crystallization from EtOAc/Hexanes to give the product as a white solid (91 mg, 32% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.67 (m, 8 H), 1.70 (s, 6 H), 2.38 (s, 3 H), 2.55 (m, 1 H), 2.77 (m, 2 H), 3.77 (m, 2 H), 4.12 (m, 1 H), 4.44 (m, 1 H), 6.97 (m 2 H), 7.35 (m, 1 H), 8.69 (s, 1 H), 9.03 (s, 1 H), 10.98 (brs, 1 H).

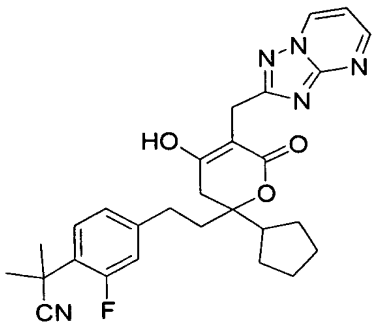
Example 18: 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile



(+ enantiomer)

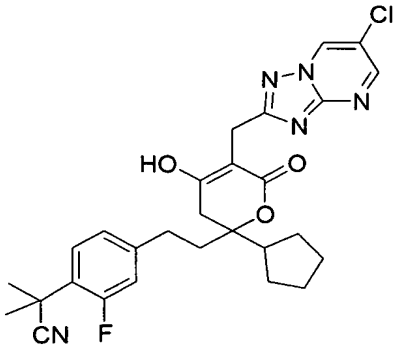
The title compound was isolated by chiral chromatography of racemic material described in Step 1 below. Conditions: Chiralpak OJ-RH, 150 x 4.6 mm, 0.6 mL/min, 30 °C; 35% acetonitrile, 65% water, 0.1% formic acid; retention time 17.6 min.

Step 1: 2-{4-[2-(2-Cyclopentyl-4,6-dioxo-5-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile



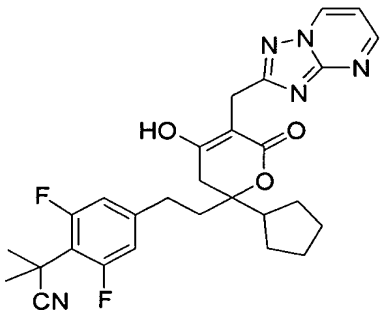
The title compound was prepared analogously to Example 1 where [1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde, prepared in step 1 from example 11, was substituted in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde in that example. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 – 1.71 (m, 8H), 1.75 (s, 6H), 2.00 (m, 2H), 2.39 (m, 1H), 2.66 (dd, *J* = 103, 18 Hz, 2H), 2.69 (m, 2H), 4.12 (s, 2H), 6.88 (d, *J* = 12.9 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 7.20 (m, 1H), 7.84 (t, *J* = 8.1Hz, 1H), 8.85 (m, 2H). MS (ESI): 504.1($M+H^+$)

Example 19: 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



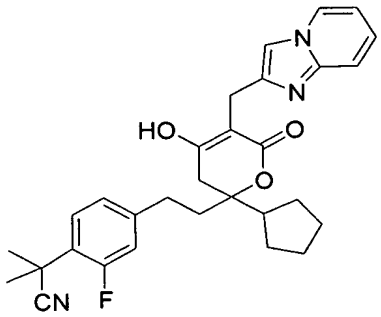
The title compound was prepared analogously to Example 1 where 6-Chloro-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde from Example 12 (step 2), was substituted in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde in the final step of that example. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 – 1.71 (m, 8H), 1.75 (s, 6H), 2.00 (m, 2H), 2.39 (m, 1H), 2.65 (dd, *J* = 101, 17.9 Hz, 2H), 2.68 (m, 2H), 4.11 (m, 2H), 6.87 (d, *J* = 11.6 Hz, 1H), 6.93 (d, *J* = 6.6 Hz, 1H), 7.35 (t, *J*= 8.3 Hz, 1H), 8.79 (s, 1H), 8.88 (s, 1H). MS (ESI): 539.1($M+H^+$).

Example 20: 2-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2,6-difluorophenyl)-2-methylpropanenitrile



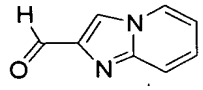
The desired product was prepared analogously to Example 7 substituting [1,2,4] Triazolo[1,5-a]pyrimidine-2-carbaldehyde in place of 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde of that example. ^{1}H NMR ($CDCl_3$) δ: 1.11 (t, *J*=7.1 Hz, 2H), 1.49-1.61 (m, 6H), 1.84 (s, 6H), 1.86-1.88 (m, 1H), 1.95-1.99 (m, 1H), 2.40-2.26 (m, 1H), 2.49 (d, *J*=17.94 Hz, 1H), 2.66 (t, *J*=8.85 Hz, 2H), 2.77 (d, *J*=17.69 Hz, 1H), 4.13 (s, 2H), 6.89 (d, *J*=10.87 Hz, 2H), 7.20 (t, *J*=6.06 Hz, 1 H), 8.85-8.87 (m, 2H). MS (ESI): 520 (M-H).

Example 21: 2-(4-{2-[2-cyclopentyl-4-hydroxy-5-(imidazo[1,2-a]pyridin-2-ylmethyl)-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)-2-methylpropanenitrile



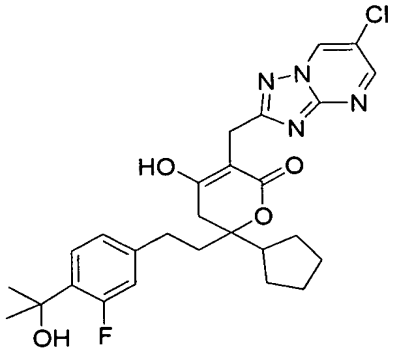
The title compound was prepared analogously to Example 1 where imidazo[1,2-*a*]pyridine-2-carbaldehyde, from step 1 below, was substituted in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde in the final step of that example. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.23-1.58 (m, 8 H), 1.60 (s, 6 H), 1.82-1.90 (m, 2 H), 2.19-2.29 (m, 2 H) 2.46-2.66 (m, 3 H), 3.50-3.63 (m, 2 H), 6.76 (t, *J*=6.31 Hz, 1 H), 6.87 (d, *J*=8.29 Hz, 1 H), 7.12 (m, 3 H), 7.32 (d, *J*=9.04 Hz, 1 H), 7.51 (s, 1 H), 8.34 (d, *J*=6.22 Hz, 1 H). Anal. Calcd. For $C_{30}H_{32}FN_3O_3.0.5H_2O$: C, 70.57; H, 6.51; N, 8.23. Found: C, 70.73; H, 6.55; N, 7.85.

Step 1: Imidazo[1,2-*a*]pyridine-2-carbaldehyde



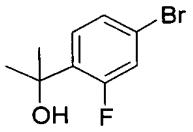
The title compound was prepared as described in J.Heterocycl.Chem.; 1992; 691-697.

Example 22: 3-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-cyclopentyl-6-{2-[3-fluoro-4-(1-hydroxy-1-methylethyl)phenyl]ethyl}-4-hydroxy-5,6-dihydro-2H-pyran-2-one



The desired product was prepared analogously to example 1, substituting 6-cyclopentyl-6-{2-[3-fluoro-4-(1-hydroxy-1-methylethyl) phenyl]ethyl} dihydro-2*H*-pyran-2,4(3*H*)-dione from Step 3 below, in place of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile and 6-chloro[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde, from example 12 (step 2) in place of 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.44 (s, 6 H), 1.52-1.70 (m, 8 H), 1.96-2.10 (m, 2 H), 2.37-2.42 (m, 1 H), 2.55-2.64 (m, 3 H), 2.74-2.80 (m, 1 H), 3.73-3.86 (m, 2 H), 5.17 (s, 1 H), 6.88-6.93 (m, 1 H), 6.99-7.02 (m, 1 H), 7.47-7.52 (m, 1 H), 8.86 (d, *J*=3.0 Hz, 1 H), 9.58 (d, *J*=3.0 Hz, 1 H). Anal: calcd for $C_{27}H_{30}ClFN_4O_4.0.9H_2O$: C, 59.48; H, 5.88; N, 10.28. Found: C, 59.52; H, 5.86; N, 9.90.

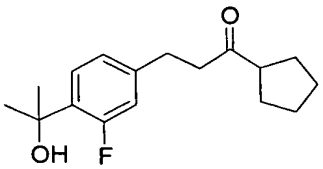
Step 1: Preparation of compound 2-(4-bromo-2-fluorophenyl)propan-2-ol



A solution of 4-bromo-2-fluorobenzoic acid (10 g) in anhydrous MeOH (200 mL) was added conc. sulfuric acid (0.5 mL). The mixture was heated to reflux for 15 hours before it was cooled down to room temperature. The solvent was removed and the residue was taken up in EtOAc (100 mL) and washed with sat. $NaHCO_3$, brine and dried over Na_2SO_4. The crude product was taken into next step without further purification.

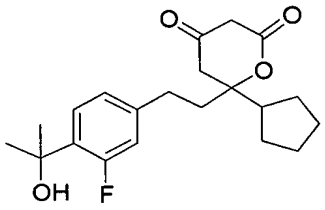
To a solution of methyl 4-bromo-2-fluorobenzoate (12 g, 51.5 mmol) in anhydrous ether (140 mL) at 0 °C was added MeMgBr (3.0 M, 70 g) drop wise. The mixture was slowly warmed up to room temperature and stirred for 3 hours. The reaction was quenched by the addition of saturated NH_4Cl and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and evaporated to dryness. The mixture was purified by flash column chromatography (0-20 % EtOAc in hexanes) to give the product (12 g, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62 (s, 6 H), 7.18-7.23 (m, 1 H), 7.25-7.28 (m, 1 H), 7.44-7.49 (m, 1 H).

Step 2: Preparation of compound 1-cyclopentyl-3-[3-fluoro-4-(1-hydroxy-1-methylethyl) phenyl]propan-1-one



To a solution of 2-(4-bromo-2-fluorophenyl)propan-2-ol (5.8 g, 25.0 mmol), from step 1 above, in anhydrous NMP (63 mL) was added 1-Cyclopentyl-2-propen-1-ol (3.15 g, 25.0 mmol), $NaHCO_3$ (4.2 g, 50 mmol) and $PdCl_2(PPh_3)_2$ (350 mg, 2 mol%). The mixture was heated to 140 °C for 4 hours before it was cooled down to room temperature. The reaction was diluted with aqueous NH_4Cl, extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and evaporated to dryness. The mixture was purified by flash column chromatography (10-50 % EtOAc in hexanes) to give the product (2.5 g, 36% yield). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.56-1.82 (m, 8 H), 1.62 (s, 6 H), 2.74-2.78 (m, 2 H), 2.82-2.89 (m, 2 H), 6.84-6.88 (m, 1 H), 6.93-6.95 (m, 1 H), 7.40-7.44 (m, 1 H).

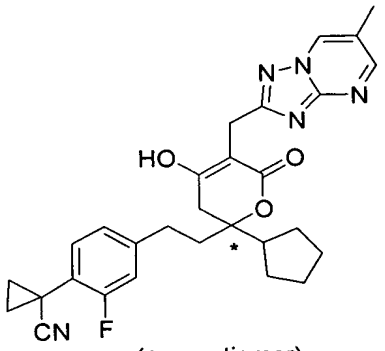
Step 3: 6-cyclopentyl-6-{2-[3-fluoro-4-(1-hydroxy-1-methylethyl) phenyl]ethyl} dihydro-2*H*-pyran-2,4(3*H*)-dione



To a solution of methyl acetoacetate (3.9 mL, 36.0 mmol) in anhydrous THF (90 mL) at 0°C was added NaH (60%, 1.44 g, 36.0 mmol) portionwise. After 10 min, the solution was cooled further to –40 °C. n-BuLi (1.6 M, 22.5 mL) was added drop wise and the resulting solution was stirred at that temperature for 30 min. A solution of 1-cyclopentyl-3-[3-fluoro-4-(1-hydroxy-1-methylethyl)phenyl]propan-1-one (2.5 g, 9.0 mmol), from step 2 above, in THF (4 mL) was added and the mixture was slowly warmed up to 25 °C and stirred for 4 hours. The reaction was quenched by the addition of NH_4Cl and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was removed and the crude product was taken directly into next step without further purification.

The crude product from previous step was dissolved in THF (40 mL) and the solution was treated with 2.0 N NaOH (18 mL). The resulting mixture was stirred at 25 °C for 4 hours before it was quenched by the addition of 1 N HCl. The mixture was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was removed and the crude product was purified by column chromatography to give the desired product in 58% yield (two steps). ^1H NMR ($CDCl_3$) δ: 1.43-1.77 (m, 8 H), 1.62 (s, 6 H), 1.92-1.99 (m, 2 H), 2.23-2.32 (m, 1 H), 2.64-2.71 (m, 2 H), 2.75-2.78 (m, 2 H), 3.41-3.45 (m, 2 H), 6.81-6.84 (m, 1 H), 6.90-6.92 (m, 1 H), 7.44-7.48 (m, 1 H).

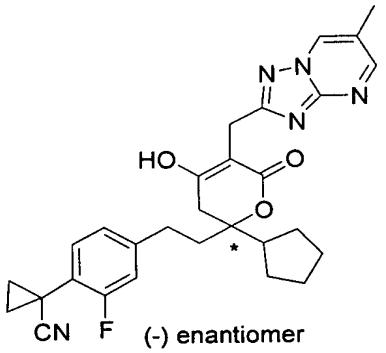
Example 23: 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile



(+ enantiomer)

The title compound was prepared by using chiral SFC to separate the racemic example Example 10 . Optical rotation determined to be (+).

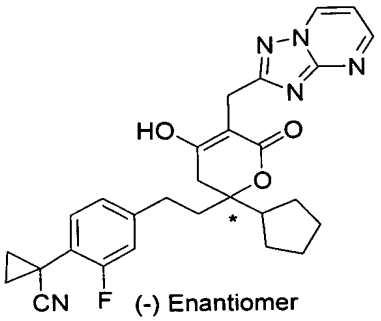
Example 24: 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile



(-) enantiomer

The title compound was prepared by using chiral SFC to separate the racemic example Example 10 . Optical rotation determined to be (-).

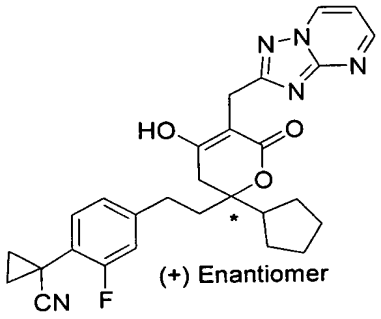
Example 25: 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile



(-) Enantiomer

The title compound was prepared by using chiral SFC to separate the racemic example 11. Optical rotation determined to be (-).

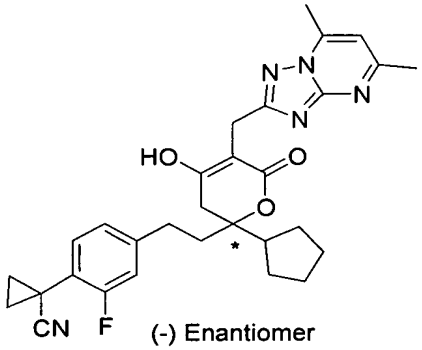
Example 26: 1-(4-{2-[2-cyclopentyl-4-hydroxy-6-oxo-5-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-3,6-dihydro-2H-pyran-2-yl]ethyl}-2-fluorophenyl)cyclopropanecarbonitrile



(+) Enantiomer

The title compound was prepared by using chiral SFC to separate the racemic example 11. Optical rotation determined to be (+).

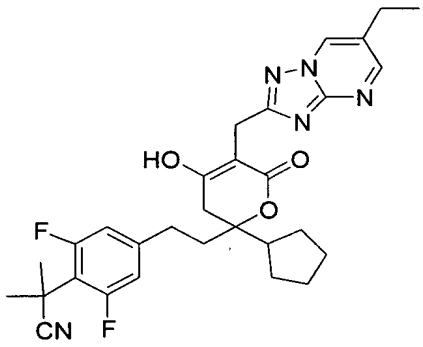
Example 27: 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile



(-) Enantiomer

The title compound was prepared by using chiral SFC to separate the racemic 1-(4-{2-[5-(6-Chloro-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl]-ethyl}-2-fluoro-phenyl)-cyclopropanecarbonitrileExample 3: Optical rotation determined to be (-).

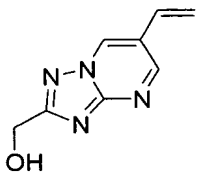
Example 28: 2-[4-(2-{2-cyclopentyl-5-[(6-ethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile



A solution of 2-{4-[2-(2-Cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-2,6-difluoro-phenyl}-2-methyl-propionitrile (272 mg, 0.7 mmol) from step 5 in example 7, in anhydrous MeOH (1.5 mL) was treated with 6-ethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (324 mg, 2.0 mmol), from step 3 below, followed by borane-dimethylamine complex (191.7 mg, 1.05 mmol) at room temperature. The reaction was stirred for 12 hours. The precipitate was removed by filtration, and the filtrate was concentrated to a crude oil. The crude oil was purified by flash chromatography (25g SiO_2, 1:3 :1:0 (93.5% ethyl acetate, 6% methanol, 0.5% acetic acid) : (81.5% hexanes, 12% ethyl acetate, 6% methanol, 0.5% acetic acid)) to give product as an oil. It was further purified by preparatory HPLC. Yield: 19.0 mg, 8.0 %. ^{1}H NMR ($CDCl_3$) δ: 1.37 (t, *J*=3.75 Hz, 3H)), 1.48-1.75 (m, 8H), 1.84 (s, 6H), 1.91-

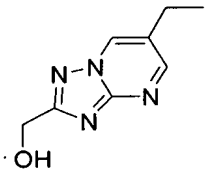
2.02 (m, 2H), 2.32-2.49 (m, 3H), 2.61-2.70 (m, 2H), 2.79-2.86 (m, 2H), 4.10 (s, 2H), 6.69 (d, *J*=10.86 Hz, 2H), 8.62 (s, 1H), 8.73 (s, 1H). MS (ESI): 548 (M-H).

Step 1: 6-Vinyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol



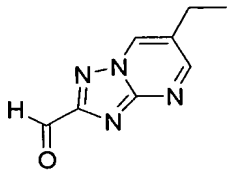
To a slurry of (6-chloro-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol (5.0g, 27.09 mmol) from step 1 , example 12, in toluene(100 mL) was added n-$Bu_3SnCHCH_2$ (9.45g, 29.79 mmol) and with catalytic $PdCl_2(dppf)_2$ (1.97g, 10% mmol). The mixture solution was refluxed overnight and then cooled to room temperature. The solution was concentrated and purified by flash chromatography (2% MeOH in CH_2Cl_2) to give the desired product as light white solid (3.4g, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.98 (d, J=6.22 Hz, 2H), 5.60 (m, 1H), 5.92 (m, 1H), 7.75 (m, 1H), 8.59 (d, J=2.26 Hz, 1H), 8.70 (d, J=2.45 Hz, 1H). MS (ESI^+), 177 (M+H)

Step 2: 6-Ethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol



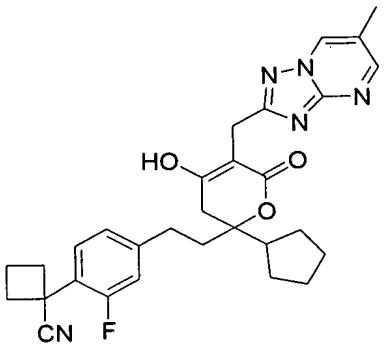
A suspension of the (6-Vinyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol (1.0 g, 5.68 mmol) from step 1 above, and 10% Pd on carbon (200 mg) in MeOH were stirred under an atmosphere of hydrogen for 16 hours. The catalyst was filtered and the solvent was removed in vacuo to afford the desired product (820 mg, 82%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.35 (t, J=7.54, 3H), 2.80 (5.60 (q, J=7.54, 2H), 4.98 (d, J=6.22, 2H), 8.59 (d, J=2.26 Hz, 1H), 8.70 (d, J=2.45 Hz, 1H). MS (ESI+) 179 (M+H)+

Step 3: 6-chloro[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde



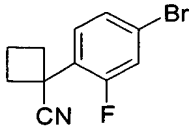
The title compound was prepared analogously to Example 12 (step 2), where 6-Ethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-methanol from step 2 above was substituted in place of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile in that example. Product was a white solid (450 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 10.25 (s,1H), 8.86 (d, J= 2.26 Hz), 8.71(d, J=2.26, 1H) 2.86(q, J=7.54, 2H), 1.45 (t, J=6.22, 3H). MS (ESI+) 177 (M+H)+

Example 29: 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclobutanecarbonitrile



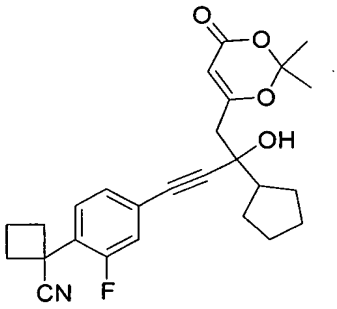
A solution of 1-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-cyclobutanecarbonitrile (0.58 g, 1.53 mmol) from step 3 below, in anhydrous MeOH (6 mL) was treated with 6-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (0.324 g, 2.0 mmol), from Example 4 (step 2), followed by borane-dimethylamine complex (118 mg, 2.0 mmol) at room temperature. The reaction was stirred for 2 hours, and the solids were filtered away. The organic liquid was concentrated to a thick oil, and then purified by flash chromatography (50g SiO_2, 3:10 -> 3:5 (93.5% ethyl acetate, 6% methanol, 0.5% acetic acid): (81.5% hexanes, 12% ethyl acetate, 6% methanol, 0.5% acetic acid)) to give the desired product as an oil. It was further purified by crystallization from ethyl acetate / hexanes to give a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54-1.82 (m, 8H), 2.01-2.13 (m, 3H), 2.38-2.48 (m, 2H), 2.48-2.57 (m, 4H), 2.67-2.77 (m, 4H), 2.82-2.85 (m, 1H), 2.88 (d, *J* = 6.06 Hz, 2H), 4.19 (s, 2H), 6.92 (dd, *J*1 = 11.62 Hz, *J*2 = 1.26 Hz, 1H), 6.99 (d, *J* = 8.08 Hz, 1H), 7.17 (t, *J* = 7.96 Hz, 1H), 8.69 (s, 1H), 8.78 (d, *J* = 1.52 Hz, 1H).

Step 1: 1-(4-Bromo-2-fluoro-phenyl)-cyclobutanecarbonitrile



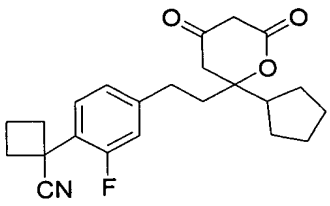
A solution of (4-bromo-2-fluoro-phenyl)-acetonitrile (4.0g, 18.7 mmol) from step 1, example 1 and 1,3-dibromopropane (2.1 mL, 20.6 mmol) in Et_2O (5 mL) was slowly added to a slurry of NaH (1.64g, 41.1 mmol, 60% in mineral oil) in DMSO (19 mL) at room temperature, being careful to keep the temperature below 35 degrees Celsius. The reaction was stirred for 2.5 hours, and then poured into 150 mL of saturated ammonium chloride. To this mixture was added $CH2_2Cl_2$, and the layers were separated. The aqueous layer was extracted with 2 x 50 mL of CH_2Cl_2, and the organic layers were combined. After drying the liquid over $MgSO_4$, the solids were filtered away, and the organic was concentrated to an oil. It was further purified by flash chromatography (90g SiO_2, 1:99 -> 1:20 (EtOAc / Hexanes) to give the desired product (2.81g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.06–2.16 (m, H), 2.51-2.63 (m, H), 2.66-2.76 (qd, *J* = 9347 Hz, 2H), 2.86-2.94 (m, 2H), 7.16-7.22 (t, *J* = 8.21 Hz, H), 7.30-7.41 (m, 2H).

Step 2: 1-{4-[3-Cyclopentyl-4-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2-fluoro-phenyl}-cyclobutanecarbonitrile



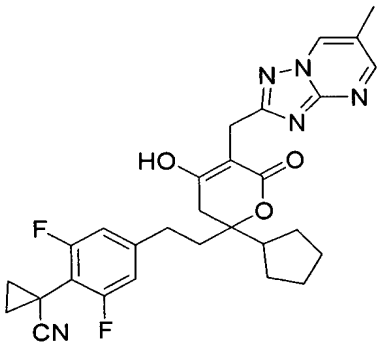
The title compound was prepared analogously to Example 1 (step 3), where 1-(4-Bromo-2-fluoro-phenyl)-cyclobutanecarbonitrile from step 1 above, was substituted in place of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile of that example. MS (ESI): 438.0 ($M+H^+$).

Step 3: 1-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-cyclobutanecarbonitrile



To a solution of 1-{4-[3-cyclopentyl-4-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2-fluoro-phenyl}-cyclobutanecarbonitrile (6.0g, 13.7 mmol) from step 2 above was added $Pd(OH)_2/C$ (2.0g) and ethanol (100 mL). The reaction was placed under a nitrogen atmosphere using a balloon filled with hydrogen. The slurry was stirred vigorously for 18 hours. The reaction was filtered to remove all of the solids, and the liquid was concentrated to an oil. The oil was dissolved in methanol (100 mL), and solution of NaOH (1.64g, 41 mmol) dissolved in water (30 mL). The reaction was stirred for 18 hours, and then acetic acid (1 mL) was added. The liquid was concentrated to an oil, then redissolved in CH_2Cl_2, and washed with 1 N HCl. The organic layer was dried over $MgSO_4$, filtered, and then concentrated to give the desired product (4.338g, 83%). MS (ESI): 382 ($M-H^+$).

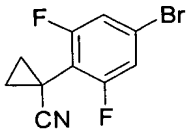
Example 30: 1-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]cyclopropanecarbonitrile



The desired product was prepared analogously to Example 7, substituting 1-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2,6-difluoro-phenyl} cyclopropanecarbonitrile from step 3 below, in place of 2-{4-[2-(2-Cyclopentyl-4, 6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2,6-difluoro-phenyl}-2-methyl-propionitrile, and 6-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde, prepared in Example 4 (step 2) instead of the 5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde of that example. Yield: 18.0 mg, 5.0 %. ^1H NMR ($CDCl_3$) δ: 1.34 (t, *J*=2.50 Hz, 2H), 1.63-1.74 (m, 9H), 1.81-1.91 (m, 2H),

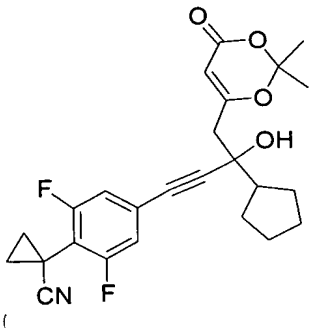
2.36-2.44 (m, 4H), 2.49 (s, 3H), 2.64-2.74 (m, 4H), 4.10 (s, 2H), 6.70 (d, *J*=7.4 Hz, 2H), 8.62 (d, *J*=2.3 Hz, 1H), 8.70 (d, *J*=2.2 Hz, 1H). MS (ESI): 532 (M-1).

Step 1: 1-(4-Bromo-2, 6-difluoro-phenyl)-cyclopropanecarbonitrile



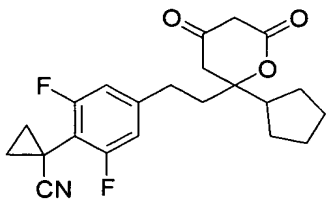
The desired product was prepared analogously to step 1 in example 3, substituting (4-Bromo-2, 6-difluoro-phenyl)-acetonitrile prepared in step 2 of example 7 instead of (4-bromo-2-fluoro-phenyl)-acetonitrile of that example. Yield: 1.07g, 74.4%. ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, 2.8 Hz, 2H), 1.77 (t, *J*=2.7 Hz, 2H), 7.13 (d, *J*=6.8 Hz, 2H).

Step 2: 1-{4-[3-Cyclopentyl-4- (2,2-dimethyl-6-oxo-6H- [1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2,6-difluoro-phenyl}-cyclopropanecarbonitrile



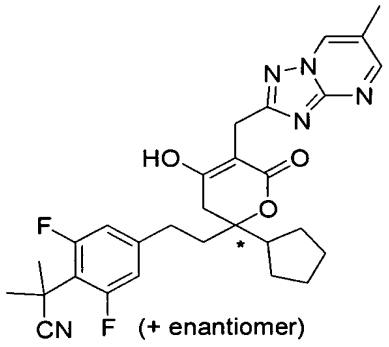
The title compound was prepared analogously to Example 1(step 3), where -(4-Bromo-2, 6-difluoro-phenyl)-cyclopropanecarbonitrile from step 1 above was substituted in place of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile of that example. Yield: 1.20g, 80.0%. ^{1}H NMR ($CDCl_3$) δ: 1.37 (t, *J*=2.8 Hz, 2H), 1.62-1.70 (m, 6H), 1.72 (s, 3H), 1.73 (s, 3H), 1.74-1.83 (m, 4H), 2.22-2.27 (m, 1H), 2.66 (s, 2H), 5.44 (s, 1H), 6.92 (d, *J*=8.0 Hz, 2H). MS (ESI): 440 (M-1).

Step 3: 1-{4-[2-(2-Cyclopentyl-4, 6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2,6-difluoro-phenyl}-cyclopropanecarbonitrile



The title compound was prepared analogously to Example 1(step 4)where 1-{4-[2-(2-Cyclopentyl-4, 6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2,6-difluoro-phenyl}-cyclopropanecarbonitrile from step 2 above, was substituted in place of 2-{4-[3-cyclopentyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxybut-1-ynyl]-2-fluorophenyl}-2-methylpropanenitrile of that example. Yield: 0.43 g, 42 %. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, *J*=2.8 Hz, 2H), 1.56-1.73 (m, 10H), 1.92 (t, *J*=4.45 Hz, 2H), 2.21-2.30 (m, 1H), 2.65-2.79 (m, 4H), 3.44 (d, *J*=5.6 Hz, 2H), 6.71(d, *J*=8.6 Hz, 2H). MS (ESI): 386 (M-1).

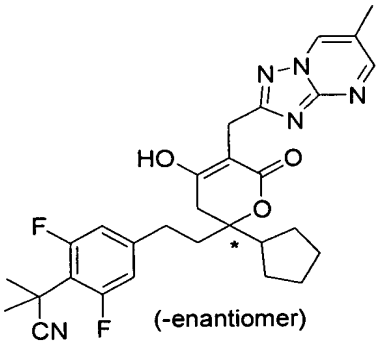
Example 31: 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile



(+ enantiomer)

The title compound was isolated by chiral chromatography of racemic material described in Example 13: . Condition: ChiralPac AS-H column, 250x4.6 mm, 120 bar, 30% MeOH, 50 mL/min, retention time 4.84 min.

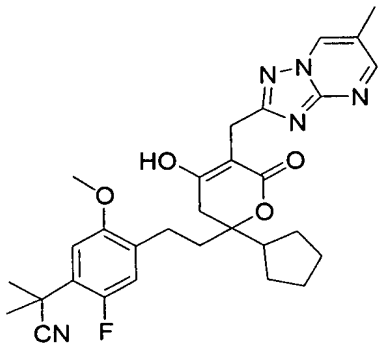
Example 32: 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile



(-enantiomer)

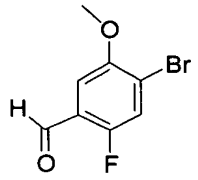
The title compound was isolated by chiral chromatography of racemic material described in Example 13: . Condition: ChiralPac AS-H column, 250x4.6 mm, 120 bar, 30% MeOH, 50 mL/min, retention time 2.85 min.

Example 33: 2-[4-(2-{2-cyclopentyl-4-hydroxy-5-[(6-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluoro-5-methoxyphenyl]-2-methylpropanenitrile



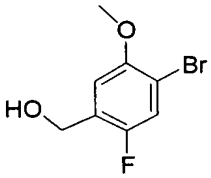
The desired product was prepared analogously to Example 7, substituting 2-{4-[2-(2-Cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-2-fluoro-5-methoxy-phenyl}-2-methyl-propionitrile from step 7 below, in place of 2-{4-[2-(2-Cyclopentyl-4, 6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2,6-difluoro-phenyl}-2-methyl-propionitrile, and 6-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde, prepared in step 2 of Example 4, instead of the 5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde of that example. Yield: 0.071 g, 16%. ^{1}H NMR ($CDCl_3$) δ: 1.54-1.63 (m, 4H), 1.77 (s, 6H), 1.91-1.97 (s, 4H), 2.37-2.45 (m, 1H), 2.48 (s, 3H), 2.57-2.80 (m, 4H), 3.75-3.85 (m, 5H), 4.10 (d, *J*=5.5 HZ, 2H), 6.84 (d, *J*=2.1 Hz, 1H), 6.89 (d, 6.6 Hz, 1H), 8.62 (d, *J*=2.3 Hz, 1H), 8.69 (d, *J*=2.2 Hz, 1H). MS (ESI): 546 (M-1).

Step 1: 4-Bromo-2-fluoro-5-methoxy-benzaldehyde



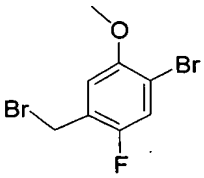
Bromine (15 ml, 300 mmol) was added slowly to a solution of 2-Fluoro-5-methoxy-benzaldehyde (23.12 g, 150 mmol) in chloroform (500 ml), and the mixture was stirred at room temperature for 5 days. The mixture was poured into water (200 ml) and extracted with chloroform (2X 200 mL). The organics were washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (2-16 % EtOAc in hexanes) to give the product. Yield: 20.7 g, 60 %. ^1H NMR ($CDCl_3$) δ: 3.93 (s, 3H), 7.08-7.13 (m, 1H), 7.29 (d, *J*=12.4 Hz, 1H).

Step 2: (4-Bromo-2-fluoro-5-methoxy-phenyl)-methanol



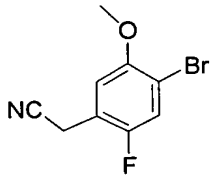
To a solution of 4-Bromo-2-fluoro-5-methoxy-benzaldehyde (4.03 g, 17.33 mmol) from step (1) below in Methanol at 0°C was added $NaBH_4$ (0.65 g, 17.33 mmol). After the reaction mixture was stirred at 0°C for 2 hours, it was allowed to warm to room temperature. The organic layer was taken up in ethyl ether, washed with water and dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (25-45% EtOAc in hexanes) to give the product. Yield: 3.90 g, 99.0 %. ^1H NMR ($CDCl_3$) δ: 3.90 (s, 3H), 4.74 (d, J=6.02 Hz, 2H), 6.82 (d, *J*=6.1 Hz, 1H), 7.29 (d, *J*=10.58 Hz, 1H).

Step 3: 1-Bromo-4-bromomethyl-5-fluoro-2-methoxy-benzene



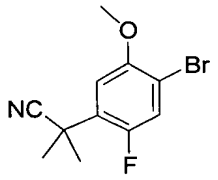
A solution of (4-Bromo-2-fluoro-5-methoxy-phenyl)-methanol, from step 2 above and 30 wt% of hydrogen bromide in acetic acid was stirred at room temperature for 90 minutes before it was poured into 80 ml of water. The mixture was extracted with pentane (3 X 50 ml) and the combined organic layers were washed with water (3 X 20 ml), dried over $MgSO_4$ and concentrated at low pressure to afford the desired product. Yield: 2.45 g, 82.2 %. ^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 3H), 4.40 (s, 2H), 6.82 (d, *J*=5.8 Hz, 1H), 7.24 (d, *J*=10.58 Hz, 1H).

Step 4: (4-Bromo-2-fluoro-5-methoxy-phenyl)-acetonitrile



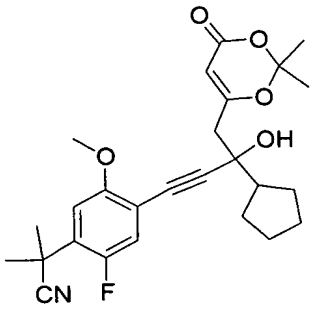
The desired product was prepared analogously to Example 1 step 1, substituting 1-Bromo-4-bromomethyl-5-fluoro-2-methoxy-benzene from step 3 above in place of 4-bromo-1-bromomethyl-2-fluoro-benzene of that example. Yield: 2.26 g, 99.9%. ^{1}H NMR ($CDCl_3$) δ: 3.74 (s, 2H), 3.91 (s, 3H), 6.95 (d, *J*=6.4 Hz, 1H), 7.35 (d, *J*=4.6 Hz, 1H).

Step 5: 2-(4-Bromo-2-fluoro-5-methoxy-phenyl)-2-methyl-propionitrile



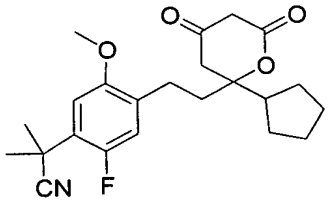
The desired product was prepared analogously to Example 1, step 2, substituting (4-Bromo-2-fluoro-5-methoxy-phenyl)-acetonitrile (1.95g, 8.0 mmol) from step 4 above in place of (4-bromo-2-fluoro-phenyl)-acetonitrile. Yield: 8.72g, 96.0%. ^{1}H NMR ($CDCl_3$) δ: 1.34 (s, 6H), 3.92 (s, 3H), 7.06 (d, *J*=6.8 Hz, 1H), 7.33 (d, *J*=10.6 Hz, 1H).

Step 6: 2-{4-[3-Cyclopentyl-4-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2-fluoro-5-methoxy-phenyl}-2-methyl-propionitrile



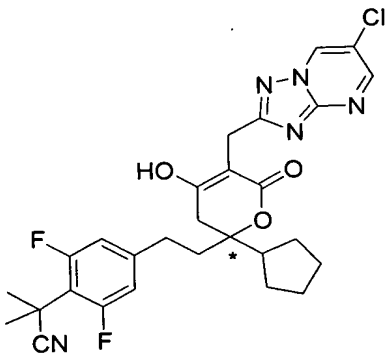
The title compound was prepared analogously to Example 1(step 3), where 2-(4-Bromo-2-fluoro-5-methoxy-phenyl)-2-methyl-propionitrile from step 5 above was substituted in place of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile of that example. Yield: 8.72g, 96.0%. ^{1}H NMR ($CDCl_3$) δ: 1.50-1.61 (m, 8H), 1.72 (s, 3H), 1.75 (s, 3H), 1.80 (s, 6H), 2.20-2.29 (m, 1H), 2.61 (s, 1H), 2.65 (d, *J*=9.1 Hz, 2H), 3.87 (s, 3H), 5.53 (s, 1H), 7.00 (d, *J*=6.5 Hz, 1H, 7.03 (d, *J*=11.6 Hz, 1H). MS (ESI): 454 (M-1).

Step 7: 2-{4-[2-(2-Cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-2-fluoro-5-methoxy-phenyl}-2-methyl-propionitrile



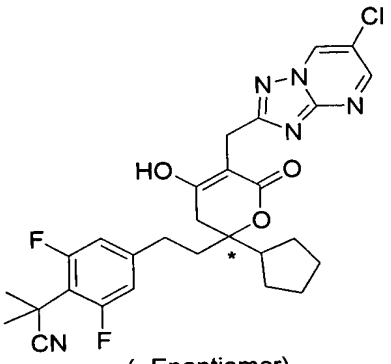
The title compound was prepared analogously to Example 1(step 4)where 2-{4-[3-Cyclopentyl-4-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-3-hydroxy-but-1-ynyl]-2-fluoro-5-methoxy-phenyl}-2-methyl-propionitrile from step 6 above, was substituted in place of 2-{4-[3-cyclopentyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxybut-1-ynyl]-2-fluorophenyl}-2-methylpropanenitrile of that example. Yield: 0.87 g, 49 %. ^{1}H NMR ($CDCl_3$) δ: 1.39-1.48 (m, 2H), 1.59-1.68 (m, 5H), 1.79 (s, 6H), 1.83-1.95 (m, 3H), 2.30-2.37 (m, 1H), 2.54-2.69 (m, 4H), 3.83 (s, 3H), 5.30 (s, 1H), 6.86 (d, *J*=11.9 Hz, 1H), 6.95 (d, *J*=6.6 Hz, 1H). MS (ESI): 400 (M-1).

Example 34: 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile



The title compound was isolated by chiral chromatography of racemic material described in Example 12: Conditions: ChiralPac AS-H column, 250x20 mm, 110 bar, 30% MeOH, 2.5 mL/min, retention time min.

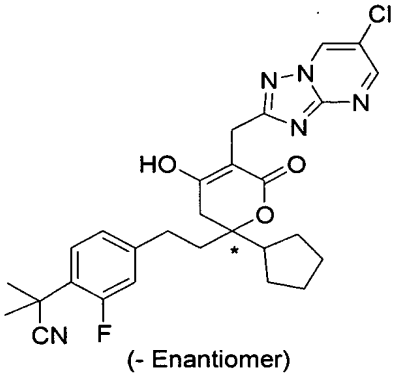
Example 35: 2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2,6-difluorophenyl]-2-methylpropanenitrile



(- Enantiomer)

The title compound was isolated by chiral chromatography of racemic material described in Example 12: Conditions: ChiralPac AS-H column, 250x20 mm, 110 bar, 30% MeOH, 2.5 mL/min, retention time 3.31 min.

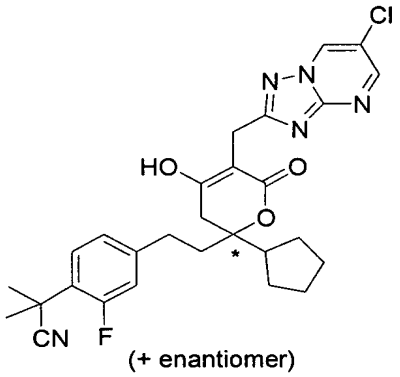
Example 36: (-)-2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



(- Enantiomer)

The title compound was isolated by chiral chromatography of racemic material described in Example 19: Conditions: ChiralPac AS-H column, 250x20 mm, 110 bar, 30% MeOH, 2.5 mL/min. Optical rotation, determined to be (-)

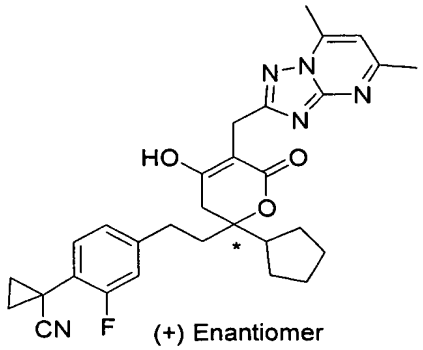
Example 37: (+)-2-[4-(2-{5-[(6-chloro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-2-cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]-2-methylpropanenitrile



(+ enantiomer)

The title compound was prepared by using chiral SFC to separate the racemic Example 19 Optical rotation determined to be (+).

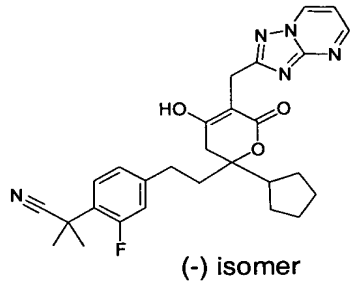
Example 38: 1-[4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl}ethyl)-2-fluorophenyl]cyclopropanecarbonitrile



(+) Enantiomer

The title compound is prepared by using chiral SFC to separate the racemic 1-(4-{2-[5-(6-Chloro-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl]-ethyl}-2-fluoro-phenyl)-cyclopropanecarbonitrileExample 3: .

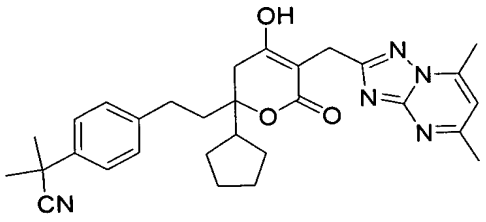
Example 39: (-)-2-{4-[2-(2-Cyclopentyl-4,6-dioxo-5-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile



(-) isomer

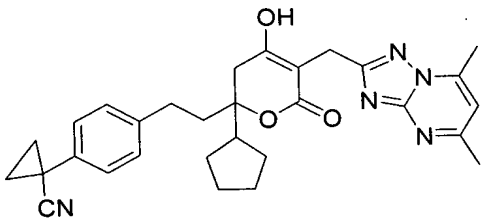
The title compound was isolated by chiral chromatography of racemic material described in Step 1 from example 18. Conditions: Chiralpak OJ-RH, 150 x 4.6 mm, 0.6 mL/min, 30 °C; 35% acetonitrile, 65% water, 0.1% formic acid; retention time 21.7 min.

Example 40: 2-(4-{2-[2-Cyclopentyl-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-ethyl}-phenyl)-2-methyl-propionitrile



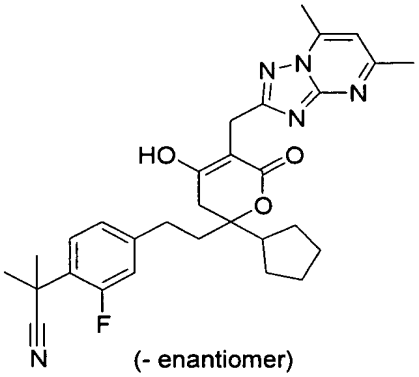
The desired product is prepared analogously to example 1, substituting 2-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl}-2-methyl-propionitrile in place of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile of that example.

Example 41: 1-(4-{2-[2-Cyclopentyl-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-ethyl}-phenyl)-cyclopropanecarbonitrile



The desired product is prepared analogously to example 1, substituting 1-{4-[2-(2-Cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-phenyl}-cyclopropanecarbonitrile in place of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile of that example.
MS (ESI): 512 (M+H).

Example 42: (-)-2-(4-{2-[2-Cyclopentyl-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]-ethyl}-2-fluoro-phenyl)-2-methyl-propionitrile

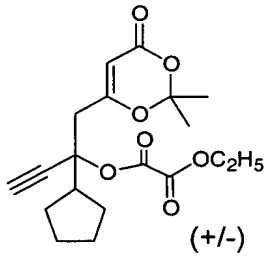


(- enantiomer)

The desired product was prepared analogously to example 1, substituting (-)-2-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile from Step 3 below, in place of 2-{4-[2-(2-cyclopentyl-4,6-dioxo-tetrahydro-pyran-2-yl)-ethyl]-2-fluoro-phenyl}-2-methyl-propionitrile of that example. ^{1}H NMR (400MHz, DMSO-d_6): δ 1.25-1.57 (m, 8H), 1.72 (s, 6H), 2.11-2.17 (m, 2H), 2.50-2.56 (m, 8H), 2.63-2.65 (m, 2H), 2.78(d, *J* = 16 Hz, 1H), 3.71(d, *J* = 16 Hz, 1H), 3.84 (d, *J* = 16 Hz, 1H), 7.06 (s, 1H), 7.17-7.23 (m, 2H), 7.36-7.42 (m, 1H), 10.88 (s, 1H). Anal. Calcd. For $C_{30}H_{34}FN_5O_3 \cdot 0.3$ EtOAc: C, 65.15; H, 6.57; N, 12.55. Found: C, 66.86; H, 6.59; N, 12.21. MS(ESI): 532 $(M+H)^+$.

The desired compound can also be separated from racemic 2-(4-{2-[2-Cyclopentyl-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]-ethyl}-2-fluoro-phenyl)-2-methyl-propionitrile . (100 mg) using chiral HPLC (Chiralpak AS-RH, 150 x 4.6 mm, 0.6 mL/min, 50% CAN, 50% H_2O, 30 °C). (38 mg, 76 % recovery, 7.536 min retention time).

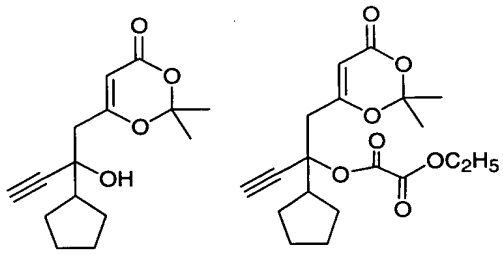
Step 1: Preparation of compound 1-cyclopentyl-1-[(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)methyl]prop-2-ynyl ethyl oxalate



(+/-)

To a solution of racemic 6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (10 g, 37.9 mmol) in CH_2Cl_2 (200 ml) was added triethylamine (3.0 eq, 113.7 mmol) at 0 °C. Then ethyl chlorooxoacetate (3.0 eq, 113.7 mmol) in CH_2Cl_2 (10 ml) was added drop wise over a 30-minute period under argon. The solution was allowed to stir overnight at room temperature. After removal of solvent, the crude product was purified using a flash column (heptane: EtOAc, 3:1) to afford the desired oxalate (13.5 g, >95%). API-MS: $[M+Na^+]$: 387;

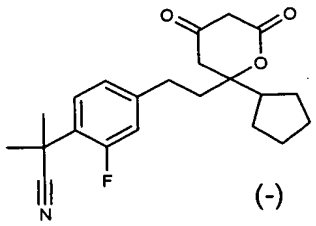
Step 2: Preparation of compound (-)-6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one



(-) (+)

To a 250 ml three-necked flask equipped with a pH electrode was added 72 ml of phosphate buffer (pH 4.0, 0.5M) and *Candida rugosa* lipase (5 g, Amano AY). The mixture was stirred vigorously and then the racemic oxalate (from step 1 below, 6 g) in 18 ml of acetonitrile was added. The reaction mixture was allowed to stir at 23 °C and the pH was kept at 4.0 using a pH titrator. The reaction was monitored with HPLC and stopped after 50% conversion (<20 hrs). The mixture was extracted by MTBE (x3) and the combined organic layer was dried over $MgSO_4$. After removal of the solvent, the crude product was separated carefully by silica-gel chromatography, using heptane/EtOAC, which afforded 2.6 g of the oxalate (+ enantiomer, 43% yield, 96% ee) and 2.0 g of product (- enantiomer, 46% yield, 92% ee). ^1H NMR (300 MHz, $CDCl_3$) : δ 1.45-1.80 (m, 8 H), 1,72 (s, 3 H), 1.74 (s, 3 H), 2.13-2.18 (m, 1 H), 2.49 (s, 1 H), 2.56 (s, 1H), 2.58 (s, 2 H), 5.43 (s, 1 H).

Step 3: Preparation of compound (-)-2-{4-[2-(2-cyclopentyl-4,6-dioxotetrahydro-2*H*-pyran-2-yl)ethyl]-2-fluorophenyl}-2-methylpropanenitrile.



(-)

The title compound was prepared analogously to Example 1(step 4)where (-)-6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one from step 2 above, was substituted in place of racemic 6-(2-cyclopentyl-2-hydroxybut-3-ynyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one in step 3 of that example. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.60-1.73(m, 6 H), 1.92-1.98 (m, 2 H), 2.22-2.30 (m, 1 H), 2.65-2.71 (m, 2 H), 2.75-2.80 (m, 2 H), 6.88-6.96 (m, 2 H), 7.37-7.43 (m, 1 H).

Method for determining inhibition of cytochrome P450 2D6: Compounds of interest at 0.3 μM, 1 μM, 3 μM, 10 μM, and 30 μM concentrations, 8 μM dextromethorphan and 1 mM NADPH were incubated with human liver microsomes (0.25 mg/mL protein and 0.075 μM P450) at 37°C for 20 min. Following the 20 min incubation, the reaction was quenched by addition of 200 μL acetonitrile containing 0.1 μM buspirone as an internal standard. The samples were then vortex mixed and centrifuged to pellet the protein. The supernantant was transferred, dried under nitrogen flow and reconstituted in mobile phase. A 10 uL aliquot was injected onto a gradient reversed phase HPLC system with a Phenomenex Luna C18 (50 x 4.6 mm) column. Dextrorphan, formed by the metabolism of dextromethorphan by CYP 2D6, was monitored using tandem MS/MS in the APCI mode with the MRM transition of *m/z* 258.3 > 156.6. Remaining-CYP2D6 activity (%) was determined for the samples relative to a vehicle control. The data were analyzed by non-linear regression according to $\%R = \% R_{max} \bullet (1-(C/(C+IC_{50})))$ using WinNonLin (version 4.0.1), where %R is the % remaining CYP 2D6 activity relative to the vehicle control, C is the concentration of the compound of interest, and IC_{50} is the inhibitory concentration of the compound of interest giving 50% inhibition of maximal % remaining activity. The data are reported as IC_{50}s (μM). If more than one assay was performed for a particular compound, the average IC_{50} is reported with the number of tests in parentheses.

Compound	IC_{50} (μM)
1	0.28 (3)
2	1.4
3	<0.074
4	<0.3

5	<0.074
6	0.19
7	<0.074
8	<0.074
9	<0.074
10	<0.074
11	<0.074
12	<0.074
13	<0.074
14	0.27
15	0.72
16	0.2
17	<0.074
18	0.67
19	0.16
20	<0.074
21	0.89
22	0.6
23	0.28
24	1.2
25	1.1
26	0.41
27	0.3
28	0.13
29	1.4
30	0.19
31	0.074
32	0.67
33	<0.074
34	<0.074
35	0.074